

Quality Assurance Guidelines for
Environmental Health Effects Research

Research Triangle Inst.
Research Triangle Park, NC

Prepared for

Health Effects Research Lab.
Research Triangle Park, NC

May 83

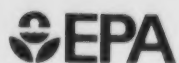


United States
Environmental Protection
Agency

Health Effects Research
Laboratory
Research Triangle Park NC 27711

EPA-600/2-83-036
May 1983

Research and Development



Quality Assurance Guidelines for Environmental Health Effects Research

PB83-221192

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TECHNICAL REPORT DATA (Please read Instructions on the reverse before completing)		
1. REPORT NO. EPA-600/2-83-036	2.	3. RECIPIENT'S ACCESSION NO. PB83 221192
4. TITLE AND SUBTITLE Quality Assurance Guidelines for Environmental Health Effects Research	5. REPORT DATE May 1983	
	6. PERFORMING ORGANIZATION CODE	
7. AUTHOR(S) P. A. Cunningham, K. W. Gold, L. E. Myers and N. H. Sexton	8. PERFORMING ORGANIZATION REPORT NO.	
9. PERFORMING ORGANIZATION NAME AND ADDRESS Research Triangle Inst. Research Triangle Park, NC 27709	10. PROGRAM ELEMENT NO. C9RA1B	
	11. CONTRACT/GRANT NO. EPA No. 68-02-3226	
12. SPONSORING AGENCY NAME AND ADDRESS Research Coordination Office Health Effects Research Laboratory US EPA RTP NC 27711	13. TYPE OF REPORT AND PERIOD COVERED Handbook	
	14. SPONSORING AGENCY CODE EPA-600/11	
15. SUPPLEMENTARY NOTES Project Officer: Ferris Benson		
16. ABSTRACT This document is a statement of the quality assurance (QA) policy of the Health Effects Research Laboratory, U. S. Environmental Protection Agency, Research Triangle Park, North Carolina (HERL-RTP). It describes the HERL-RTP QA organization and the QA responsibilities of both management and technical research personnel in relation to the mandatory Agency QA policy and project data quality requirements. It provides guidelines for managers in the implementation of Agency QA policy and evaluation of research documentation, and presents guidelines for project officers for (1) development of QA Project Plans and research protocols for intramural research and support tasks, (2) preparation of requests for proposals, (3) preaward a evaluation of extramural proposals, (4) review and evaluation of QA Program of Project Plans for extramural projects, and (5) review and evaluation of data quality officers in the development or review of QA plans are treated in detail. These guidelines are reviewed and revised annually by the HERL-RTP QA officer, the QA Committee, and HERL-RTP division directors.		
17. KEY WORDS AND DOCUMENT ANALYSIS		
a. DESCRIPTORS Quality Control Management Health Quality	b. IDENTIFIERS/OPEN ENDED TERMS Health Effects Research Quality Assurance Health Measurements Research Quality	c. COSATI Field/Group
18. DISTRIBUTION STATEMENT Release to Public	19. SECURITY CLASS (This Report) Unclassified	21. NO. OF PAGES 124
	20. SECURITY CLASS (This page) Unclassified	22. PRICE

QUALITY ASSURANCE GUIDELINES FOR
ENVIRONMENTAL HEALTH EFFECTS RESEARCH

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FOREWORD

The many benefits of our modern, developing, industrial society are accompanied by certain hazards. Careful assessment of the relative risk of existing and new man-made environmental hazards is necessary for the establishment of sound regulatory policy. These regulations serve to enhance the quality of our environment in order to promote the public health and welfare and the productive capacity of our Nation's population.

The complexities of environmental problems originate in the deep interdependent relationships between the various physical and biological segments of man's natural and social world. Solutions to these environmental problems require an integrated program of research and development using input from a number of disciplines. The Health Effects Research Laboratory, Research Triangle Park, NC and Cincinnati, OH conducts a coordinated environmental health research program in toxicology, epidemiology and clinical studies using human volunteer subjects. Wide ranges of pollutants known or suspected to cause health problems are studied. The research focuses on air pollutants, water pollutants, toxic substances, hazardous wastes, pesticides, and non-ionizing radiation. The laboratory participates in the development and revision of air and water quality criteria and health assessment documents on pollutants for which regulatory actions are being considered. Direct support to the regulatory function of the Agency is provided in the form of expert testimony and preparation of affidavits as well as expert advice to the Administrator to assure the adequacy of environmental regulatory decisions involving the protection of the health and welfare of all U.S. inhabitants.

The quality of the data resulting from this research is an overriding factor in determining their usefulness to EPA. In recognition of the importance of data quality assurance, our Laboratory instituted an active, comprehensive program to coordinate the development and implementation of effective quality assurance planning into all research within the Laboratory. More recently, the Administrator has required quality assurance for all environmentally related measurement activities supported by the Agency. This substantially enhances the quality assurance aspects of our own research measurements.

This document represents the current statement of our effort. I am confident that full implementation of our data quality assurance policy, with the help of the guideline manuals and the increased application of quality assurance principles, will enhance the scientific merit of our research program.

F. Gordon Hueter, Ph.D.
Director
Health Effects Research Laboratory

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SECTION 1

ABSTRACT

This document is a statement of the quality assurance (QA) policy of the Health Effects Research Laboratory (HERL), U.S. Environmental Protection Agency, Research Triangle Park, North Carolina. It describes the HERL QA organization and the QA responsibilities of both management and technical research personnel in relation to the mandatory Agency QA policy and project data quality requirements. It provides guidelines for managers in the implementation of Agency QA policy and evaluation of research documentation, and presents guidelines for project officers for (1) specification of QA requirements for extramural and intramural tasks, (2) preparation of QA Project Plans and research protocols for intramural research and support tasks, (3) review and evaluation of QA Program and Project Plans for extramural projects, and (4) review and evaluation of data quality throughout the project term. Aspects of research projects that must be considered by project officers in the development or review of QA plans are treated in detail. These guidelines are reviewed and revised annually by the HERL QA officer, the QA Committee, and HERL division directors.

SECTION 2

INTRODUCTION

2.1 LABORATORY OBJECTIVES

The U.S. Environmental Protection Agency's (EPA) Health Effects Research Laboratory (HERL) at Research Triangle Park, North Carolina, conducts an extensive research program to evaluate the health effects of chronic and acute exposures to environmental pollutants, including air and water pollutants, pesticides, toxic substances, and nonionizing radiation. This research program presently involves two distinct areas: bioassays and human exposure studies.

Bioassays employ living organisms or living parts of organisms to measure or assay the effects of a test substance or mixture of test substances. In vivo bioassays use whole animals (e.g., rats, fish, monkeys) and in vitro bioassays use cultured tissues or individual cells (e.g., rodent lungs, white blood cells, bacteria). Specific areas of bioassay research conducted by HERL include:

- Investigations of acute and chronic effects of low level exposure of whole animals to environmental pollutants, including those to quantify the absorption, distribution, storage, mobilization, biotransformation, and excretion of environmental pollutants. The effects of pollutants upon metabolic processes in selected species are included. Effects selected relate to risk factors for acute illness, chronic disease, and reproduction. Emphasis is placed upon discerning which portions of the population may be especially susceptible to pollutant-induced or pollutant-aggravated disorders.
- Investigations of the effects of environmental pollutants upon cellular and organ model systems of human disease. Models of specific acute or chronic diseases include in vivo and in vitro models for infectious, neoplastic, and other noninfectious conditions. The morphologic and functional integrity of cellular and organ systems is used to clarify effects of environmental pollutants.
- Investigations in the fields of mutagenesis, carcinogenesis, cellular toxicology, and metabolism. The mutagenic and oncogenic potential of agents of environmental concern, including pure chemicals and complex

environmental mixtures, is evaluated through the stepwise application of bioassay methodologies including short-term prescreening tests, confirmatory short-term in vitro bioassays, and established in vivo whole animal mutagenesis and carcinogenesis bioassays.

Investigations of the functional effects of environmental pollutants, toxic substances, and nonionizing radiation on the central and peripheral nervous systems, including normal behavior patterns, electrophysiologic responses, neuroendocrine status, and appropriate performance testing. Neurophysiologic parameters chosen are those that most nearly model the relevant human experiences.

Human studies involve controlled exposure of human volunteers to sub-acute concentrations of test substances to evaluate changes in physiological, biochemical, metabolic, neurological, and behavioral responses.

2.2 BACKGROUND

Because of an increased awareness of the serious health effects of environmental pollutants and of the need for adequate data quality to support risk assessment and control strategies, HERL management initiated a Laboratory-wide data quality program in May 1976 with the issuance of a formal Quality Assurance (QA) Plan.¹ Subsequently, a QA officer was appointed and a Laboratory QA Committee was established for the purpose of designing and implementing a Laboratory-wide QA Program. QA guidelines have since been developed for management policy,² research task planning,³ and environmental pollutant measurements.^{4 5 6} Guidelines for QA in selected areas of biological research are currently being developed to continue the QA Program at HERL.

The HERL QA Program is further supported by EPA's recent commitment to a mandatory Agency-wide QA Program. Agency policy initiated by the Administrator in memoranda of May 30, 1979,⁷ and June 14, 1979,⁸ requires participation in a centrally managed QA Program of all EPA Laboratories, Program Offices, Regional Offices, and those monitoring and measurement efforts supported or mandated through contracts, regulations, or other formalized agreements. The Office of Research and Development (ORD) is responsible for developing, coordinating, and directing implementation of the Agency QA Program. Within the ORD, this responsibility has been delegated to the Quality Assurance Management Staff (QAMS) of the Office of Monitoring Systems and Technical Support.

To implement Agency policy, EPA Laboratories, Program Offices, Regional Offices, and all extramural contractors, grantees, or cooperating institutions are required to prepare QA Program Plans covering all monitoring and measurement activities that generate and process environmentally related data for Agency use.⁹⁻¹⁰ A QA Program Plan is a written document that presents in general terms the overall policies, organization, objectives, and functional responsibilities within the organization designed to achieve specified data quality goals of a particular organization (e.g., EPA Laboratory, Program Office, Regional Office, contracting organization). A QA Program Plan has been developed for HERL and approved by QAMS. This plan is reviewed and revised annually by the QA officer, the Laboratory director, and the QA Committee.

Agency policy also requires that a QA Project Plan or narrative statement be prepared for each environmentally related measurement project (or group of similar projects) conducted or supported by the Agency detailing the policies, organization, objectives, functional activities, and specific quality assurance and quality control (QC) activities designed to achieve data quality goals or requirements of the program.⁹⁻¹⁸ The QA Project Plan must address procedures used to routinely assess precision, accuracy, completeness, representativeness, and comparability of the data produced.

To facilitate compliance with Agency QA requirements, the QAMS has issued a series of QA guidelines documents for all intramural and extramural tasks.⁹⁻¹⁸ These documents are summarized in Section 4.1.

2.3 PURPOSE

The purpose of this document is to provide guidance to HERL managers and project officers in the development, implementation, and evaluation of project-level QA programs. Particular emphasis is placed on development and evaluation of QA Project Plans in accordance with current Agency requirements.¹¹

2.4 DEFINITIONS

Several terms related specifically to health effects research data quality and to the HERL QA Program are defined below as they are used in this document. More complete glossaries of data quality terminology can be found in References 4 and 19.

2.4.1 Quality

Quality is the totality of characteristics of research data that bear on their ability to satisfy previously specified criteria. For laboratory measurement systems, accuracy, precision, representativeness, and comparability are of major importance. Completeness is appropriately applied to larger systems, such as air monitoring networks. A detailed discussion of these data quality parameters is given in Section 4.2.5.

2.4.2 Quality Control

Quality control is a system of activities designed to achieve and maintain a previously specified level of quality in data collection, processing, and reporting. Quality control is performed by the task or project personnel. QC activities include control or correction for all variables affecting data quality (see Section 4.2.12).

2.4.3 Quality Assurance

Quality assurance is an external program of planned, systematic activities that are necessary to provide assurance that specified data quality criteria are achieved for any given project. The QA program involves a continuing evaluation of the adequacy and effectiveness of the overall QC program with provision for initiation of corrective action measures where necessary. QA activities consist of: (1) quantitative measurements, such as interlaboratory tests or performance audits, and (2) qualitative measures, such as site visits or systems audits, to evaluate the capability of a total measurement system to provide specified quality data.

2.4.4 Environmental or Environmentally Related Measurement

The term "environmental (or environmentally related) measurement" applies to all field and laboratory investigations that generate data involving the measurement of chemical, physical, or biological parameters in the environment, such as determining the presence or absence of priority pollutants in waste streams; health and ecological effects studies; clinical and epidemiological investigations; engineering and process evaluations; studies involving laboratory simulation of environmental events; and studies or measurements on pollutant transport and fate, including diffusion models.

2.4.5 Project

A project is any task or group of tasks encompassed in a HERL work plan, intramural or extramural, that produces or uses environmentally related data.

2.4.6 Protocol

The term protocol includes all task or project planning documents. Specifically included are research plans, support activity procedure statements, extramural work plans, scopes-of-work, and QA Project Plans.

2.4.7 Quality Assurance Program Plan

A QA Program Plan is a written document that presents in general terms the overall policies, organization, objectives, and functional responsibilities (within the organization) designed to achieve specified data quality goals of a particular organization (e.g., EPA Laboratory, Program Office, Regional Office, contracting organization).

2.4.8 Quality Assurance Project Plan

A QA Project Plan is a written document that details the policies, organization, objectives, functional activities, and specific QA and QC activities designed to achieve data quality goals or requirements of a specific measurement program. The QA Project Plan must address procedures used to routinely assess precision, accuracy, completeness, representativeness, and comparability of the data produced.

2.4.9 Quality Assurance Officer

The QA officer is that individual who is assigned the responsibility for overview and guidance of the QA Program for an organization or for a specific project. Organizationally, the QA officer should be in a position to provide independent and objective evaluation and assessment of the effectiveness of the QA Program and to provide timely feedback and recommendations.

2.4.10 Project Officer

The project officer is that individual who is assigned overall responsibility for a project from inception through completion. This responsibility covers both technical and QA aspects of the project.

2.4.11 Contracting Officer

The contracting officer is that individual who is assigned the responsibility for ensuring that contracting is done as authorized by law and regulation.

2.4.12 Quality Assurance Performance Audit

A QA performance audit is a quantitative analysis or check made with a material or device of known properties or characteristics to determine the accuracy of a measurement system. Performance audits may require the identification or the quantitation of specific elements or compounds or both.

2.4.13 Quality Assurance Systems Audit

A QA systems audit consists of a systematic, onsite, qualitative review of facilities, equipment, training, procedures, recordkeeping, data validation, data management, and reporting aspects of the total measurement system. A QA systems audit may be required (1) to assess, prior to project initiation, the capability of a measurement system to generate data of the required quality, or (2) to determine compliance of an ongoing project with specified QA requirements.

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SECTION 3

MANAGEMENT POLICY

It is the policy of the Health Effects Research Laboratory (HERL), Research Triangle Park, that all quality assurance (QA) activities will be carried out in accordance with Agency mandates and guidance specified by the Quality Assurance Management Staff (QAMS) of the Office of Research and Development (ORD). Planning for the incorporation of suitable QA measures into measurement activities is the responsibility of project officers. It is the responsibility of management to ensure that all project-related documents or plans incorporate adequate QA measures. It is also management's responsibility to ensure that QA Project Plans are implemented and that project data are of adequate and documented quality. The HERL QA organization, consisting of a QA Committee chaired by the QA officer, is available to all Laboratory technical and management personnel for consultation or active participation in development and review of QA Project and Program Plans.

3.1 QUALITY ASSURANCE PROGRAM GOALS

The goal of the HERL QA Program is to ensure, assess, and document the quality of laboratory and field data used by EPA in evaluating the health effects of pollutants and in developing adequate control strategies.

Specific objectives of the HERL QA Program are to:

- Establish a mechanism to ensure that QA Project Plans are developed and implemented for each intramural project (or group of similar projects). This will be done at the division, branch, section, or group level, as appropriate.
- Establish a mechanism to ensure that research protocols are prepared for all new intramural projects. These research protocols shall address project-specific QC procedures for each measurement method.
- Establish a mechanism to ensure that QA Project Plans or narrative statements and QA Program Plans are prepared for all new extramural projects, as required by QAMS.

- Review and approve all QA Project Plans, QA Program Plans or narrative statements, and intramural research protocols for new tasks. Recommend revisions and ensure that such revisions are made prior to approval and initiation of project activities.
- Establish a mechanism to ensure that written standard operating procedures (SOPs) are developed for all routine measurement methods and research activities.
- Establish a mechanism to ensure that SOPs, QA Project Plans, QA Program Plans, and other QA documentation are maintained under a system of document control.
- Establish and implement peer review procedures for planning, ongoing measurement activities, and technical publications.
- Maintain a central file of information on available reference and audit materials and devices for HERL measurement methods.
- Maintain written QA guidelines to assist HERL in the development of general and specific, current and future HERL research.
- Continue a program of educating all personnel within HERL in the basic concepts of quality assurance through QA workshops.
- Implement requirements that all reported data include quality estimates of precision, accuracy or bias, completeness, and, when appropriate, representativeness and comparability.
- Develop feedback and corrective action mechanisms for routinely identifying data quality problem areas, alerting management to them, and evaluating the solutions to such problems.
- Monitor the operational performance of HERL through appropriate intralaboratory and interlaboratory quality evaluation programs.
- Conduct systems and performance audits of ongoing HERL projects, as required.
- Identify additional routine measurement methods for inclusion in the HERL QA audit program.
- Establish a procedure for regular QA reports to HERL management and QAMS.

3.2 QUALITY ASSURANCE POLICIES

It is the policy of HERL that the Laboratory QA Program will be appropriate to ensure that all data collected or used are of documented quality. HERL QA Program requirements cover all activities supported or

required by HERL that generate or use environmentally related measurement data. This includes all funded projects--intramural and extramural, contract, grant, and cooperative and interagency agreement. Laboratory QA policy requires that QA considerations be included in all requests for proposals (RFPs), research proposals and evaluations, work plans, project plans, and project reports.

In accordance with Agency policy, every environmental measurement project (or group of similar projects) planned, conducted, or sponsored by HERL must have a QA Project Plan or narrative statement approved by the QA officer.¹⁻¹⁰ Specifically, the QA Project Plan ensures that: (1) the level of data quality needed will be determined and stated before the data collection effort begins; and (2) all data generated and reported will be of the quality and integrity established by the QA Project Plan. For intramural tasks, QA Project Plans are prepared for each functional organizational unit (i.e., division, branch, section, or group) within which all tasks may appropriately be regarded as a single measurement project; these plans are then included by reference in the research or support task protocols required for each intramural task (see Section 4.1.1). For extramural projects, QA Project Plans or narrative statements are prepared on an individual task or project basis. In addition, all extramural projects involving environmental measurements must include a QA Program Plan or a statement of overall QA policy.^{2 4-11}

Systems and performance audits and interlaboratory/interfield comparison studies will be conducted on measurement projects within HERL at the direction of the QA officer, the project officer, and/or the appropriate division director to assess the adherence to, and adequacy of, approved QA Project Plans and to assess the need for corrective action. External audits may also be conducted at the request of QAMS.

3.3 QUALITY ASSURANCE PROGRAM ORGANIZATION

To support project officers and management in the development and implementation of appropriate QA programs to ensure adequate data quality, the HERL QA organization is interwoven with the existing HERL management. The structure of the QA organization, the functional responsibility of QA personnel, and the lines of communication for achieving a cost-effective Laboratory QA Program are discussed below.

3.3.1 Organizational Structure for Quality Assurance

The HERL management structure is shown in Figure 3-1. All QA management responsibilities are assigned to the QA officer. The independence and objectivity of the QA Program is supported by the QA officer's organizational independence of all divisions involved in the data generation process. All divisions within HERL are covered by QA Program requirements. Interfacing of the QA organization with various levels of management is shown in Figure 3-2.

3.3.2 Assignment of Responsibilities

Although each individual involved in the generation of data is implicitly a part of the HERL QA organization, certain individuals have specific, assigned QA responsibilities. Refer to Figure 3-2 in the following discussion.

3.3.2.1 HERL Laboratory Director--

The HERL Laboratory director has overall responsibility for all Laboratory activities, including quality assurance. Because the success of the QA Program ultimately depends on the director's full support, it is his/her responsibility to enlist and encourage the cooperation of all HERL personnel in the program.

3.3.2.2 Quality Assurance Officer--

The QA officer has primary responsibility for all Laboratory QA activities and reports directly to the HERL Laboratory director. His/her responsibilities include the development, implementation, evaluation, and documentation of QA policy and procedures appropriate to the Laboratory objectives. This includes development of audit programs for Laboratory measurement programs, evaluation of the cost effectiveness of QA programs and plans, and recommendations for their improvement.

As advisor to the Laboratory director, the QA officer regularly reports on the status of the Laboratory QA Program, identifies specific needs (e.g., methods development and problem areas), and recommends specific courses of action for strengthening the program.

As chairman of the QA Committee, the QA officer initiates development of Laboratory-wide QA guidelines and procedures. He/she coordinates efforts

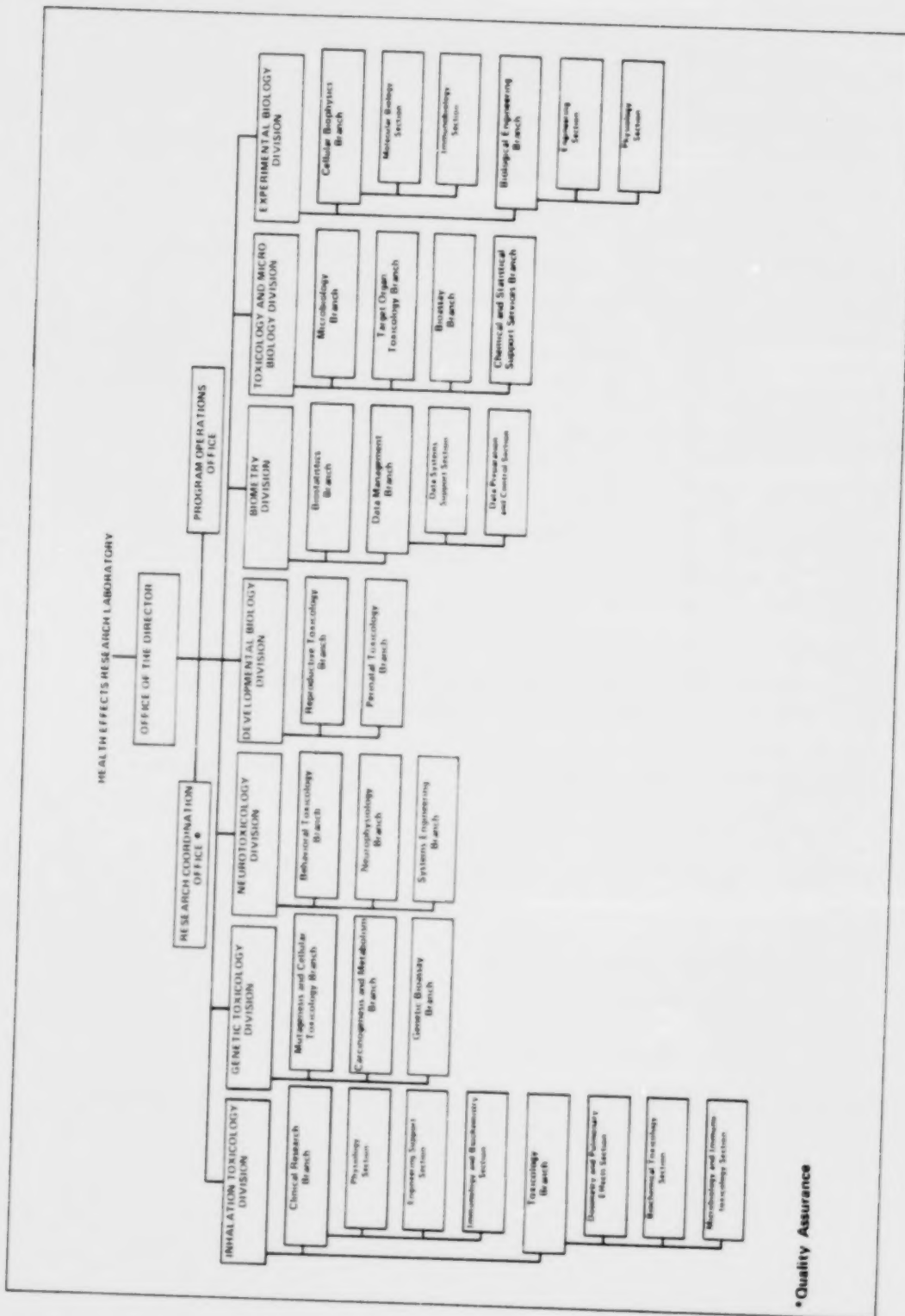


Figure 3-1. Functional management structure, HERL.

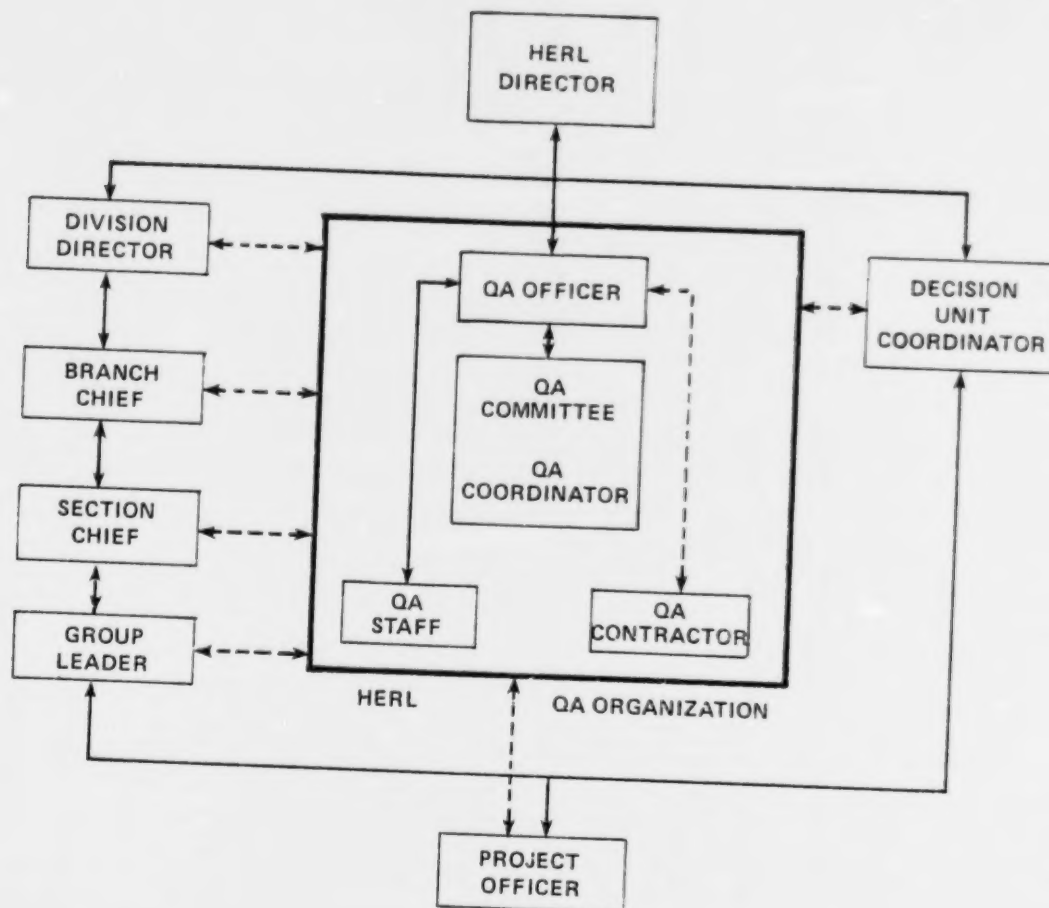


Figure 3-2. Interactions of the QA organization with other HERL management.

to develop QA procedures and materials for specific HERL research techniques and assesses data provided by the QA Committee regarding evaluation of the QA Program.

As QA consultant, the QA officer is available to consult with and recommend to the HERL professional staff (project officers, investigators, etc.) appropriate and necessary QA methods and plans for ensuring the quality of the research data produced.

Finally, since motivation of personnel is a critical factor in the success of the Laboratory QA Program, a major responsibility of the QA officer is to ensure that all personnel are fully aware of the scope and objectives of the Laboratory QA Program and understand the importance of their roles to the overall success of the program.

3.3.2.3 Quality Assurance Coordinator/Committee--

Each division director designates one or two divisional representatives to serve on the HERL QA Committee. These QA coordinators recommend and review proposals for improvements in QA policies and procedures and report and evaluate potential data quality problem areas. Within their respective divisions, the QA coordinators consult on matters of quality assurance, serve as a primary source of information on research QA considerations, review contract proposals for QA aspects, and help to implement the Laboratory QA Program.

The QA Committee serves as an advisory committee to the Laboratory director. Specifically, the Committee's functions include assisting in the evaluation and refinement of data quality objectives of the QA Program to ensure that they meet the Laboratory needs with minimum disruption of existing workloads and procedures, reviewing recommendations presented to the Committee, and assessing the effectiveness of the QA Program.

3.3.2.4 Quality Assurance Staff--

The QA staff is composed of HERL investigators who hold primary appointments in other research areas at HERL and who serve as technical consultants to the QA officer and other HERL investigators. They are responsible for providing the necessary technical expertise to ensure adequate implementation and review of the Laboratory QA Program. In particular, they are available to advise project officers and management on the technical

aspects of specific task activities that affect overall data quality (e.g., methods development) and to assist the QA officer in the development, implementation, and evaluation of audit programs for both Laboratory-wide and task-specific measurement techniques.

3.3.2.5 Quality Assurance Contractors/Consultants--

External QA contractors/consultants assist in implementing major parts of the HERL QA Program. Their responsibilities include development and/or evaluation of Laboratory QA guidelines and plans, development and implementation of Laboratory-wide audit programs, methods development, and provision of analytical services.

3.3.2.6 Decision Unit Coordinator--

Evaluation of the need for specific types of research is an essential part of the Laboratory QA Program. The decision unit coordinator is the functional manager for each general program area and, as such, is responsible for distributing resources (i.e., funding and manpower) and for evaluating the relevance of each proposal (and project) in his/her program area to the overall Laboratory and Agency goals. In addition, he/she is responsible for identifying impending needs in specific areas of research and encouraging proposals for new projects in these areas, thus aligning the production of research data with the projected Laboratory and Agency needs.

3.3.2.7 Functional Managers--

Functional managers (i.e., division director, branch chief, section chief, group leader) are responsible for ensuring the quality of all research data produced under their direction. This responsibility includes development of QA Project Plans for their organizational unit, as appropriate (see Section 3.2); review and approval of intramural research protocols; review and approval of extramural proposals, work plans, QA Project Plans or narrative statements, and QA reports; and periodic evaluation of all ongoing QA programs. Peer review of QA programs by the QA Committee may also be requested by management.

3.3.2.8 Project Officer--

As task manager, the project officer is responsible for ensuring that the technical and administrative requirements of each task are met. It is his/her responsibility to adequately ensure and document the quality of the

task results, including both the research data and conclusions. The project officer draws upon his/her professional training and expertise, in collaboration with the HERL QA organization, to determine which QA/QC techniques most appropriately apply to a particular task and to develop task-specific QA programs. For intramural projects, it is the responsibility of the project officer to prepare a detailed research protocol including all project-level QC activities and appropriate reference to the relevant division, branch, or section QA Project Plan (see Section 3.2). For extramural projects, it is the responsibility of the project officer to ensure that Agency QA requirements are met²⁻¹¹ and that the awardee develops acceptable QA Program and Project Plans as required.

To ensure adequate data quality, the project officer must obtain regular objective evaluation of data quality throughout the project term through assessment of regular internal QC checks and through external QA activities (e.g., systems and performance audits). Specific items that must be considered in data quality assessment are discussed in detail in Section 4.2.

3.4 REFERENCES

1. U.S. Environmental Protection Agency, Health Effects Research Laboratory, Research Protocols, Research Triangle Park, NC, Director's Memorandum, September 25, 1979.
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3. U.S. Environmental Protection Agency, Interim Guidelines and Specifications for Preparing Quality Assurance Project Plans, QAMS-005/80, Office of Research and Development, Washington, DC, December 1980.
4. U.S. Environmental Protection Agency, Guidelines and Specifications for Implementing Quality Assurance Requirements for EPA Contracts and Inter-agency Agreements Involving Environmental Measurements, QAMS-002/80, Office of Research and Development, Washington, DC, May 1980.
5. U.S. Environmental Protection Agency, Quality Assurance Requirements for Contracts over \$10,000, Acting Director's Memorandum, Quality Assurance Management Staff, March 29, 1982.
6. U.S. Environmental Protection Agency, Guidelines and Specifications for Implementing Quality Assurance Requirements for Research Grants Involving Environmental Measurements, QAMS-003/80/01, Office of Research and Development, Washington, DC, April 1981.

7. U.S. Environmental Protection Agency, Guidelines and Specifications for Implementing Quality Assurance Requirements for Demonstration Grants and Cooperative Agreements Involving Environmental Measurements, QAMS-003/80/02, Office of Research and Development, Washington, DC, April 1981.
8. U.S. Environmental Protection Agency, Guidelines and Specifications for Implementing Quality Assurance Requirements for State and Local Assistance Grants Involving Environmental Measurements, QAMS-003/80/03, Office of Research and Development, Washington, DC, April 1981.
9. U.S. Environmental Protection Agency, Quality Assurance Requirements for Financial Assistance, Acting Director's Memorandum, Quality Assurance Management Staff, March 30, 1982.
10. U.S. Environmental Protection Agency, Quality Assurance Requirements for Cooperative Agreements, Acting Director's Memorandum, Quality Assurance Management Staff, July 16, 1982.
11. U.S. Environmental Protection Agency, Guidelines and Specifications for Preparing Quality Assurance Program Plans, QAMS-004/80, Office of Research and Development, Washington, DC, April 1980.

SECTION 4

QUALITY ASSURANCE GUIDELINES FOR PROJECT MANAGEMENT

This section presents quality assurance (QA) guidelines for overall project management, including: (1) specification of QA requirements for extramural and intramural tasks, (2) preparation of QA Project Plans and research protocols for intramural research and support tasks, (3) review and evaluation of QA Program and Project Plans for extramural tasks, and (4) review and evaluation of data quality throughout the project term.

4.1 QA REQUIREMENTS FOR HERL PROJECTS INVOLVING ENVIRONMENTAL MEASUREMENTS

By memoranda of May 30, 1979,¹ and June 14, 1979,² the U.S. Environmental Protection Agency (EPA) Administrator established an Agency-wide QA Program to ensure that all environmentally related measurements funded or mandated by EPA and interagency agreements be scientifically valid, defensible, and of estimated precision and accuracy. The Agency has issued a series of guideline documents and memoranda¹⁻¹³ detailing specific QA requirements for different types of environmental research and measurement projects conducted by or for the EPA. Key elements of the Agency QA Program include:

1. QA Program Plans--A QA Program Plan is a written document that describes in general terms the overall policies, organization, objectives, responsibilities, and procedures designed to achieve specified data quality goals. All intramural HERL tasks are covered by the Laboratory QA Program Plan.¹⁴ QA Program Plans for extramural tasks must be prepared by the offeror/awardee in accordance with Agency guidelines.⁴ Minimum contents of a QA Program Plan include:
 - A statement of policy concerning the organization's commitment to implement a QA/QC program to ensure generation of measurement data of adequate quality to meet the requirements of the proposed work.

- An organizational chart showing the position of the QA office or officer within the organization. It is highly desirable that the QA organization be independent of the functional groups that generate measurement data.
 - A delineation of the authority and responsibilities of the QA personnel and the related data quality responsibilities of other functional groups of the organization.
 - The background and experience of the proposed QA and project personnel relevant to meet the QA requirement specifications in the proposed work.
 - A general description of the proposed approach for accomplishing the QA specifications in the project.
2. QA Project Plans--A QA Project Plan is a written document prepared by the project management describing the project organization and responsibilities and specific QA/QC activities that will be implemented to achieve specified data quality goals or requirements. At a minimum, the following items must be addressed in all required QA Project Plans:⁵
- Project description
 - Project organization and responsibility
 - Facilities, services, equipment, and supplies
 - QA objectives for measurement data
 - Sample collection
 - Sample custody
 - Calibration
 - Sample analysis
 - Recordkeeping/documentation
 - Data management
 - Internal QC checks
 - External QA audits
 - Preventive maintenance
 - Specific routine procedures for assessing data quality

- Feedback and corrective action
- QA reports to management

Each of these items is described in detail in Section 4.2. Additional assistance in addressing specific items required in the QA Project Plan may be obtained by consulting References 15 through 20, as appropriate.

Given the large number of intramural tasks conducted by HERL and the similarity of many of these tasks at the division, branch, section, or group level, present HERL policy requires the preparation of formal QA Project Plans at these levels only, as appropriate, and not for individual intramural tasks. The intent is to reduce the increasing burden of paperwork on individual project officers and to eliminate unnecessary duplication of effort in meeting QA requirements. This approach also provides a mechanism for establishing more uniform data quality assessment, feedback and corrective action, and standard operating procedures (SOPs) within HERL. It should be emphasized that research protocols, including description of specific task-level QC activities, are still required for each intramural task.^{21 22} QA activities may be referenced to the appropriate overall QA Project Plan for the operating unit (division, branch, section, or group), with specific note of any deviation from this plan.

3. External performance and systems audits--It is the responsibility of the project officer and/or the QA officer to ensure that appropriate QA audit requirements are established for each project prior to initiation of measurement activities. Intramural and extramural investigators may be required to participate in performance and systems audits as part of the preaward evaluation and/or during the period of project performance. Requirements for performance audits will depend on the availability of reference materials or devices for the measurements to be made. In general, performance audits are required where reference samples are available, unless the offeror has previously met this requirement to the satisfaction of the project officer and the QA officer. In the event that reliable reference materials or devices are not available for the measurements involved, consideration should be given to the use of common or split samples for cross-comparisons of results from offerors with those from EPA.
4. QA Reporting--Provision for adequate QA reporting for each project must also be made by the project officer and the QA officer. Projects of short duration (i.e., 1 year or less) may require only a final QA report. Projects of longer duration may require periodic (e.g., quarterly) QA reports. These QA reports should be separate from other required reports and should contain such information as:

- Changes in the QA Project Plan
- Significant data quality problems, accomplishments, and status of corrective actions
- Results of QA performance audits
- Results of QA systems audits
- Assessment of data quality in terms of precision, accuracy, completeness, representativeness, and comparability, when appropriate
- Quality-related training efforts.

Any or all of the above QA items may be required for a given project.

Many of the Agency QA guideline documents are in draft form and specific QA requirements are not yet firmly established. Therefore, to assist in QA planning, implementation, and review for both intramural and extramural tasks, the QA officer has prepared information packets for HERL project officers summarizing:

1. Current Agency and Laboratory QA requirements for
 - Intramural research tasks
 - Intramural support tasks
 - Contracts
 - Interagency agreements
 - Research grants
 - Demonstration grants
 - Cooperative agreements
 - State and local assistance grants.
2. Specific instructions for ensuring that appropriate QA requirements are met.
3. Required QA enclosures for extramural projects.

These information packets are distributed to all HERL project officers and are maintained under a system of document control so that they can be

updated as necessary to reflect changes in the Agency QA Program requirements. Project officers should refer to this information and consult with their QA Committee representative and/or the HERL QA officer to ensure that appropriate QA requirements are met for specific intramural and extramural projects.

All QA Project Plans must be reviewed and approved by appropriate HERL management prior to project funding. For intramural tasks, approval by the group leader, branch chief, division director, and QA officer of the research protocol, with reference to the appropriate division, branch, or group QA Project Plan, is required. Additionally, the project officer must review and approve all QA Program and Project Plans for extramural projects under his/her supervision. Periodic assessment of QA Project Plan implementation by the project officer and the QA officer throughout the project term provides the means by which management may determine if adequate data quality is being obtained in a cost-effective manner. Assistance from the QA organization is available to project officers and other management personnel for evaluation of QA Project Plans and the effectiveness of their implementation.

A detailed checklist of specific items that should be considered in all project-level QA planning or review is given in Figure 4-1. This checklist has been developed from current Agency guidelines for QA Project Plans⁵ and is intended to be all inclusive. The relative impact of each of the checklist items on overall data quality will vary between tasks; however, no element should ever be deleted from consideration. For example, the precision of a measurement process is always estimable by repeating the process under appropriate conditions. However, for some of the biological or health-related environmental research involving microorganisms, tissue cultures, animals, or human subjects, it may be difficult to design accuracy checks for all aspects of a basic research study. Since much of this work is of a developmental nature, calibration techniques or standard reference materials may not be readily available. In other cases, subjective evaluation of changes in tissue or cellular morphology must be made based on human judgment. In these instances, intensive peer review of research protocols or work plans may be the best or only means of evaluating research objectives prior to project initiation, ensuring collection of data of known and adequate

QA/QC Items	Comments
<u>Identification</u>	
() Documentation control	
() Title page with provision for approval signatures	
() Table of contents	
<u>Project Description</u>	
() Objectives	
() Hypotheses	
() Experimental design	
() Data analysis	
() Duration	
() End use of data	
<u>Project Organization and Responsibilities</u>	
() Project line authority	
() QA authority	
() Key personnel	
() Training	
() Résumés	
<u>Facilities and Services</u>	
() Appropriateness to task requirements	
() Environmental aspects (e.g., temperature, lighting, ventilation)	
() Maintenance (preventive and corrective)	
() Inspection procedures	
() Configuration control	
() Security	
() Safety provisions	
() Support services	
<u>Equipment</u>	
() Appropriateness to task requirements	
() Maintenance (preventive and corrective)	
() Configuration control	
() Safety provisions	
() Recordkeeping (i.e., documentation of calibration and maintenance history)	
<u>Supplies</u>	
() Certification	
() Acceptance screening	
() Animal care and testing procedures	
() Storage	
() Stockroom tracking system	

Figure 4-1. Checklist for project-level QA/QC planning and evaluation.

QA Objectives for Measurement Data

Comments

- () Accuracy _____
- () Precision _____
- () Completeness _____
- () Representativeness _____
- () Comparability _____

Sample Collection

- () Site selection _____
- () Documentation of sampling procedure _____
- () Flow charts or diagrams _____
- () Sample identification _____
- () Sample storage and handling _____
- () Standardized data formats and recordkeeping _____

Sample Custody

- () Field custody _____
- () Laboratory custody _____
- () Evidentiary considerations _____

Calibration

- () Standards _____
- () Procedures _____
- () Frequency _____
- () Corrective action _____

Sample Analysis

- () Criteria for methods selection _____
- () Documentation of analytical procedures _____

Recordkeeping

- () Documentation control _____
- () Standardized data forms _____
- () Storage _____
- () Security _____

Data Management

- () Data collection _____
- () Data storage and backup _____
- () Data transfers _____
- () Data validation _____
- () Data reduction _____
- () Software QA/QC _____
- () Data analysis _____
- () Reporting _____

Figure 4-1. (continued)

Internal QC Checks	Comments
() Systems audits	
() Performance audits	
— replicates	
— spiked samples	
— split samples	
— blanks	
— internal standards	
— QC samples	
— surrogate samples	
— calibration standards	
() Control charts	
() Reagent checks	
<u>External QA Audits</u>	
() Systems audits	
() Performance audits	
<u>Preventive Maintenance</u>	
() Procedures	
() Frequency	
() Documentation	
<u>Specific Routine Procedures for Assessing Data Quality</u>	
() Equations used to calculate precision and accuracy	
<u>Feedback and Corrective Action</u>	
() Management line authority	
() Corrective action reporting	
<u>QA Reports to Management</u>	
() Specification of contents	
() Frequency of reporting	
() Review and approval authority	
<u>Special Requirements</u>	
() Radiation safety form	
() Toxic chemical form	
() Request for animal procurement and care	
(√) Satisfactory	
(U) Unsatisfactory	
(NA) Not Applicable	

Figure 4-1. (continued)

quality during project performance, and assessing final project data and conclusions after completion of the project.

Project-level QA programs should also include good laboratory practice (GLP) concepts where appropriate. The Food and Drug Administration's (FDA) GLP Regulations¹⁸ apply to nonclinical studies performed on animals, plants, microorganisms, or subparts thereof. The EPA's proposed GLP Standards¹³ (summarized in Figure 4-2) are intended for use in the development of data on the health effects of chemical substances and mixtures tested in accordance with Section 4 of the Toxic Substances Control Act.¹⁹ The proposed EPA GLPs generally apply to all bioassay laboratory health effects studies conducted by or on behalf of manufacturers of chemical substances.

4.2 ELEMENTS OF A QA PROJECT PLAN

The QA elements described in the following sections must be addressed in every QA Project Plan. The relative impact of each of these elements on overall data quality will vary greatly between projects; however, no element should ever be deleted from consideration.

4.2.1 Identification

4.2.1.1 Document Control--

Each QA Project Plan must be prepared under a system of document control. One recommended system employs a standardized document control format and provides for convenient replacement of pages that may need to be changed within the technical procedures descriptions.^{20 23} This document control format requires, in the top right corner of each page, the section number, revision number, date (of revision), and page number as shown below:

Section No. 2.12
Revision No. 0
Date: September 27, 1977
Page 1 of 5

A digital numbering system identifies sections and subsections within the text. New subsections should begin on a new page. This format groups together the pages within a subsection to allow for its revision or expansion without necessitating reissue of the complete document. Each time a new page is added or expanded within a section, the number of the preceding

Summary of Proposed EPA GLPs for Health Effects Research

1. The proposed GLPs apply to studies relating to health and safety evaluations conducted under Section 4 of the Toxic Substances Control Act, whether conducted by the sponsor or under contract or grant. Fourteen terms are defined in this section.
2. Test and control substances must be characterized by strength, purity, composition, and stability before initiation of a study. Their containers must be labeled by name, chemical abstract number or code number, batch number (expiration date), and storage conditions requirements. Handling procedures must ensure proper identification and minimize contamination, deterioration, or damage. Mixtures must be suitably analyzed to characterize their uniformity, concentration, and stability; expiration date is that of the earliest expiring component.
3. An ample number of personnel having adequate and documented education, training, and/or experience must be available to the study. Their personal habits, health, and clothing must be appropriate for their assigned duties. The designated study director ensures that all provisions of the GLPs are fulfilled for the study. The QA unit independently assures management, at least every 3 months, that the facilities, equipment, personnel, methods, practices, records, and controls conform with GLP requirements, in each phase of the study.
4. Facilities must be of suitable size, construction, and location to facilitate proper conduct of the study. For animal studies, animals must be properly separated, isolated, and quarantined. Separate areas are required for:
 - Biohazardous substances
 - Diagnosis, treatment, and control of known or suspected laboratory animal diseases
 - Sanitary disposal
 - Feed, bedding, supplies, and equipment
 - Handling of test and control substances and their mixing
 - Routine procedures
 - Administrative and personnel use
 - Secure archival of raw data and specimens
5. Equipment must be suitably designed and located for operation, inspection, cleaning, maintenance, and calibration according to written procedures; written records are kept to document these operations.

Figure 4.2. Summary of EPA's proposed GLPs for health effects research.¹³

6. Testing facility operation must be by written SOPs for (as a minimum):

- Animal room preparation
- Animal care
- Test and control substance handling
- Test system observations
- Laboratory tests
- Handling of moribund/dead animals
- Necropsy
- Specimen collection and identification
- Histopathology
- Data handling, storage, and retrieval
- Equipment maintenance and calibration
- Transfer, placement, and identification of animals

All deviations must be authorized by the study director and documented in the raw data. Each laboratory must have immediately available, suitable laboratory manuals and SOPs, both active and historical. Reagents and solutions must be labeled to indicate identity, concentration, storage requirements, and expiration date. SOPs for animal care include housing, feeding, handling, care, receiving quarantine, health parameters, and identification. In addition, periodic feed and water analysis must be documented as part of the raw data; cages and racks must be cleaned at appropriate intervals. Bedding, cleaning materials, and pest controls must be documented as noninterfering in the study.

7. Minimum protocol specifications must be given. The conduct of the study is detailed in terms of the protocol, specimen identity, records, and data recording.
8. Reserved
9. Reserved.
10. Minimum contents of the final report must be outlined. Archival of all raw data, protocols, specimens, and final reports is detailed. Indexed, orderly, and secure storage is required for at least 10 years.

Appendix A

Additional guidelines are given as follows:

Figure 4-2 (continued)

Handling of test substances: DHEW's "Guidelines for the Laboratory Use of Toxic Substances Posing a Potential Occupational Carcinogenic Risk" and IARC's "A Manual on the Safety of Handling Carcinogens in the Laboratory."

Handling of radioactive materials: NRC's Title 10 of CFR.

Administrative and personal facilities: OSHA's Title 29 of CFR.

Animal care and handling: HEW's "Guide for the Care and Use of Laboratory Animals."

Animal care facilities: HEW's "Guide for the Care and Use of Laboratory Animals," and 9 CFR Part 3.

Figure 4-2 (continued)

page should be included and a letter added to it. Revisions may also be promulgated by issue of entirely new documents. In the case of minor revisions, pen-and-ink posting on the original document with the action noted on the revision notice may be sufficient. The QA officer or QC coordinator should be responsible for distributing documents and/or revisions and for obtaining the required signatures.²⁰ A record of all revisions made to a document should be maintained to derive full benefit of document control techniques.

In general, a QA program should include a system for updating formal documentation of all operating procedures. The most important elements of a QA program to which documentation control is applied include procedures for: sample collection, storage, and handling; calibration; sample analysis; data collection and reporting; auditing; data management including data transfers, data reduction, analysis, and validation (including programmed checks when data processing is computerized); and preventive maintenance.

To ensure that all changes to project documentation are incorporated efficiently, maintenance of full control over the distribution of such documents is essential. A central file should be established within the organization including such information as: document number, title, branch originating the document, latest issue date, change number, distribution list, and signatures of persons acknowledging receipt. Whenever a revision is made, the group responsible for maintaining the file should issue the revision, with a revision notice. Obsolete documents (or pages of documents) should be removed from all files and points of use, returned to the central file, logged in, and destroyed. The group responsible should have sole authority to destroy obsolete documents except for one set of originals and revisions.

4.2.1.2 Title Page with Provision for Approval Signatures--

4.2.1.2.1 Intramural. A sample title page for a QA Project Plan for intramural tasks is shown in Figure 4-3. The title page should include:

- Document control number
- Specification of the HERL organizational unit(s) covered by the QA Project Plan (i.e., division, branch, section)

DOCUMENT CONTROL
NUMBER

QUALITY ASSURANCE PROJECT PLAN

Project Organization
Division, Branch, or Section

HERL APPROVALS

BRANCH CHIEF:	_____	Date:	_____
DIVISION DIRECTOR:	_____	Date:	_____
LABORATORY DIRECTOR:	_____	Date:	_____
QA OFFICER:	_____	Date:	_____

Figure 4-3. Sample title page for intramural QA Project Plan.

- Provision for approval signatures by the branch chief, division director, Laboratory director, and the HERL QA officer.

Completion of reviews and approvals is shown by signatures on the title page. Copies of the approved QA Project Plan should be filed with the QA officer and distributed by the project officer to all task personnel who have a major responsibility for ensuring the quality of the measurement data.

4.2.1.2.2 Extramural. A sample title page for a QA Project Plan for extramural research is shown in Figure 4-4. The title page should include:

- Document control number
- Name and address of contracting organization conducting project
- Project number
- Project title
- Provision for approval signatures by the extramural organization's project manager and QA coordinator and by the HERL project officer and QA officer.

Completion of reviews and approvals is shown by signatures on the title page. A copy of the approved QA Project Plan should be distributed by the extramural organization's project manager to all task personnel who have a major responsibility for the quality of the measurement data. Copies should also be filed with the HERL project officer and QA officer.

4.2.1.3 Table of Contents--

The table of contents for all QA Project Plans must include all items shown in Figure 4-5.

A distribution list for all branch, division, section, or group level HERL QA Project Plans (i.e., those for intramural projects) should include: division director, branch chief, section chief, group leader, all project officers within the originating unit, and the QA officer.

The distribution list for all HERL extramural projects should include: EPA project officer, EPA QA officer, project manager/principal investigator, QA coordinator, and key project personnel.

DOCUMENT CONTROL
NUMBER

QUALITY ASSURANCE PROJECT PLAN

Name and address of extramural project
organization conducting research

Project Number

Project Title:

EXTRAMURAL ORGANIZATION APPROVALS

PRINCIPAL INVESTIGATOR/
PROJECT MANAGER:

Date: _____

QA COORDINATOR:

Date: _____

HERL APPROVALS

PROJECT OFFICER:

Date: _____

QA OFFICER:

Date: _____

Figure 4-4. Sample title page for extramural QA Project Plan.

SECTION	PAGE
Project Description	
Project Organization and Responsibilities	
Facilities, Services, Equipment and Supplies	
QA Objectives for Measurement Data	
Sample Collection	
Sample Custody	
Calibration	
Sample Analysis	
Recordkeeping	
Data Management	
Internal Quality Control Checks	
External QA Audits	
Preventive Maintenance	
Specific Routine Procedures for Assessing Data Quality	
Feedback and Corrective Action	
Quality Assurance Reports to Management	
Appendixes (e.g. , Standard Operating Procedures, Résumés)	

Distribution List:

Intramural Projects:

- Division Director
- Branch Chief
- Section Chief
- All project officers within the originating unit
- QA Officer

Extramural Projects:

- EPA Project Officer
- EPA QA Officer
- Project Supervisor (project manager/principal investigator)
- Project QA coordinator
- Key project personnel

Figure 4-5. Sample table of contents for QA Project Plan.

4.2.2 Project Description

A detailed project description is essential to provide QA reviewers with sufficient information to evaluate the proposed project and to determine if QA/QC efforts are properly placed and timed. In any HERL project that involves data collection and analysis, it is important to consult a statistician during the initial planning phases of the study and throughout data collection and analysis. An analysis plan, no matter how ingenious, cannot compensate for poor experimental design.

For HERL division, branch, section, or group QA Project Plans, the project description should include a summary statement of that unit's overall research activities. Individual project or task descriptions for intramural projects should be included in the written protocol required for each study.^{21 22} For extramural projects, a detailed project description must be included in the QA Project Plan, either in full or by reference to the work plan. Items to be addressed in the project description include:

- A statement of objectives and hypotheses to be tested
- A description of the experimental design including the variables to be measured, sample sizes, experimental materials, conditions, and instruments
- An outline of the method of data analysis to be used
- Anticipated duration of the project
- Intended use(s) of the acquired data

4.2.2.1 Objectives and Hypotheses to be Tested--

A clearly written, concise statement of the research objectives allows precise formulation of the specific hypotheses to be tested. It is advisable to rank these objectives. The reference population to which the results are to apply should be clearly defined.

4.2.2.2 The Experimental Design--

The study design should include a clear definition of all relevant variables to be considered, the study subjects (e.g., bacteria, animals, cell culture lines, humans), the number of subjects (sample size), and the data to be collected and the methods to be used in sampling and analysis.

It is essential that there be a clear understanding between the project officer and an extramural organization as to the level of accuracy and precision required for any measurements made. Further, from the outset of a project it should be clear to all concerned whether the emphasis is on (1) reproducibility and comparability of measurements, as when data will come from many laboratories or will be compared to historical data obtained by specific methodology; (2) meeting regulatory requirements, as when the data must be able to stand up in court; or (3) methods development to design a more specific or more accurate measurement. Misunderstandings in these areas could result in the generation of otherwise valid data that may be useless in meeting the goals of a particular project.

Measurement processes must be carefully characterized and validated^{24 25} before being routinely used in any HERL projects. Any hypothesized property of the measurement system, such as linearity of the relation between measured and true values, constancy of precision across varied levels or conditions, or bounds on bias and imprecision, should be confirmed under the conditions (e.g., locale, personnel, equipment) where they will be applied. Although biases are often difficult to ascertain in health effects research where reference materials are not available, it is always possible to study precision.

A well-designed testing program should consider the following:²⁶

1. Are all the relevant intrinsic factors (e.g., age, size, weight, sex, reproductive condition) and extrinsic environmental factors (e.g., temperature, duration of exposure, light-dark cycle, chemical form of the pollutant tested, synergistic interactions) being considered?
2. Are the effects of the relevant variables adequately distinguishable from the possible effects of other variables?
3. Has the possibility of interaction between variables been anticipated and accounted for?
4. Is the study design as free of bias as possible?
5. Is the study design consistent with the stated objectives? Will the project yield adequate data (degrees of freedom) to estimate parameters of interest with a reasonable precision? Are sample sizes justified on the basis of precision using historic or conjectured estimates of variances?

6. Is the study design cost effective? Would a more limited design provide sufficient data at a lower cost?
7. Does the design make adequate provision for controls (negative, positive, and solvent comparison groups)?
8. Is the design logistically sound? (Are adequate time, space, personnel, etc., available to properly perform the checks necessary to ensure the specified data quality?)

4.2.2.3 Data Analysis--

The research protocol should cover in some detail the proposed method of statistical analysis and the assumed underlying mathematical/probabilistic model. Quality assurance for data analysis primarily involves assuring the assumptions and accuracy of computations used to estimate parameters.

4.2.2.4 Anticipated Duration of Project--

The QA Project Plan should contain a statement of the proposed startup and completion date for the proposed project.

4.2.2.5 Intended Use(s) of Acquired Data--

A brief statement describing the intended use of the data collected in the project should be provided.

4.2.3 Project Organization and Responsibility

4.2.3.1 Project Line Authority--

For all QA Project Plans, a project organization chart should be provided clearly identifying key individuals, including the QA officer, who are responsible for ensuring the collection of data of documented quality. In all extramural projects, the line authority between HERL and the extramural organization as well as line authority within the extramural organization, including the extramural organization's QA coordinator or officer, should be identified. A sample project organization chart is shown in Figure 4-6.

4.2.3.2 Personnel--

All personnel participating in research-related activities under the auspices of HERL should possess experience and knowledge adequate to perform the technical tasks assigned. Personnel qualifications should be reviewed and evaluated by the project officer and may be reviewed by the QA officer.

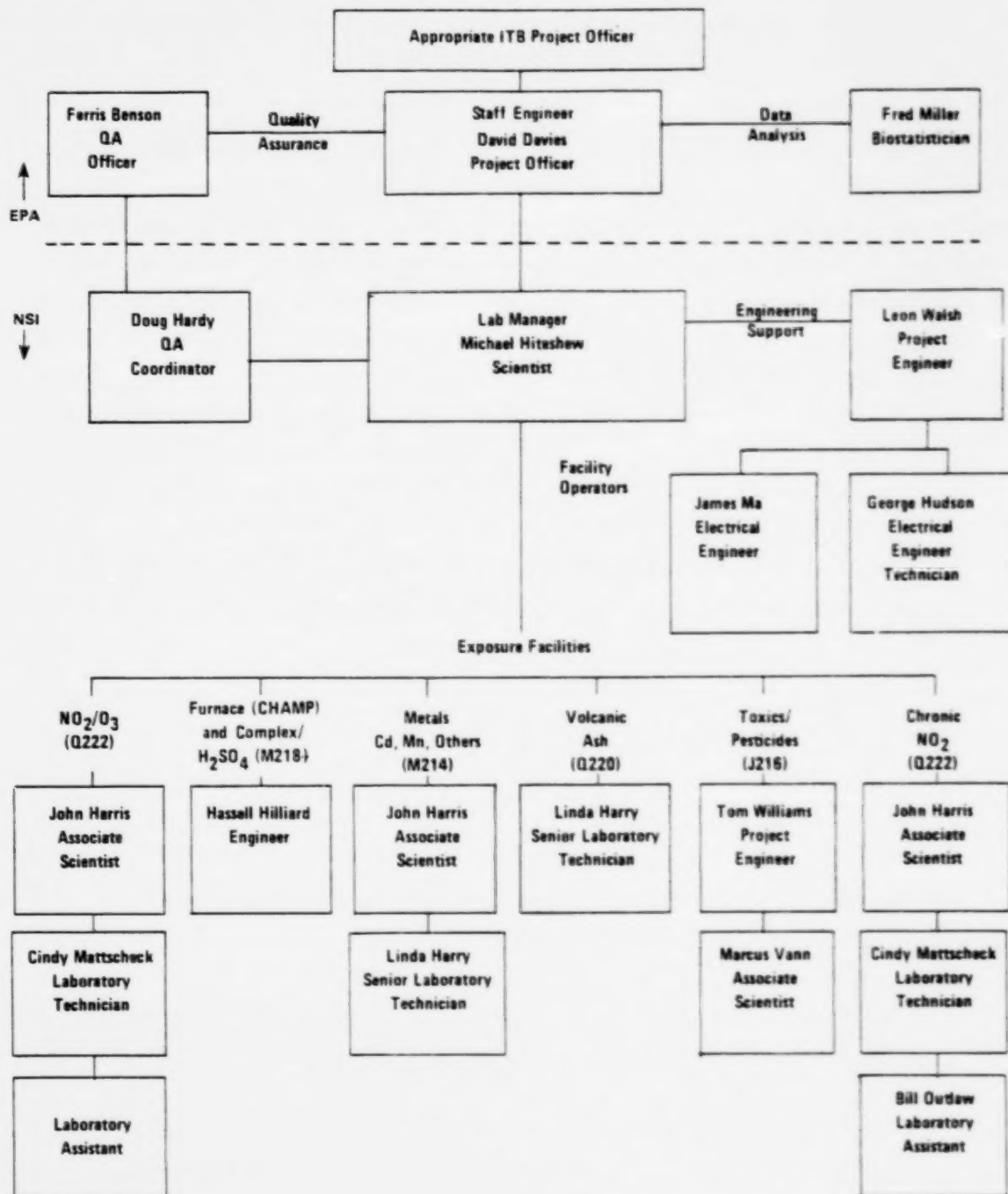


Figure 4-6. Sample project organization chart.²⁷

Professional résumés of key task personnel should be included in the appendix of QA Project Plans or in the research protocol.

4.2.3.3 Training--

A statement in the QA Project Plan should indicate that the key task personnel have experience in or have received training in performance of the specific technical task for which they have responsibility in the project. Where appropriate, personnel should be expected to participate regularly in certification programs, including external audit programs for performance evaluation and/or accredited training courses in their areas of specialization. All project personnel should keep abreast of current developments in their fields of expertise. Periodic meetings during project implementation may be helpful in information exchange and lead to improved quality control.

Bench-level personnel should also be involved in the feedback and corrective action loop (Section 4.2.16.2). This involvement should begin early in the project with a briefing on the overall task goals, methods to be employed, and personnel roles in quality assurance.

4.2.4 Facilities, Services, Equipment, and Supplies

Evaluation of project-specific facilities, support services, equipment, and supplies is the responsibility of the project officer in cooperation with the HERL QA organization. The QA officer may, at his/her option or at the request of the project officer, division director, branch chief, or section chief, inspect and evaluate or request an audit by qualified personnel of facilities, support services, equipment, and supplies used by laboratories performing HERL-supported work.

4.2.4.1 Facilities--

All HERL-supported facilities should be capable of producing acceptable data quality in an efficient, cost-effective manner with minimum risk to personnel.

The suitability of a facility for the execution of both the technical and QA aspects of a project may be assessed prior to use through a systems audit by qualified technical and QA personnel. These audits should determine if facilities are of adequate size, with satisfactory lighting, ventilation, temperature, noise levels, and humidity, and if they are operation-

ally consistent with their designed purpose. Satisfactory personnel safety and health maintenance features should also be present. HERL requires that all facilities meet acceptable safety and health standards.²⁸

Facility security should be tailored to the project research needs and to personnel safety requirements. Security may range from areas available for common use by nonproject personnel to restricted areas accessible only to authorized project personnel.

Authorization and documentation of all changes in facility configuration should be limited to a single professional staff member (e.g., project officer) who is qualified to ensure that necessary modifications will not jeopardize data quality or personnel health and safety within the facility.

4.2.4.2 Support Services--

The reliability of required support services is of primary importance in evaluating the project facilities and should be checked by periodic (regular) performance audits. Numerous measurement processes depend on routine services (i.e., gases, electricity, heat, steam, or water) and loss of these may cause significant deterioration of data production or quality. Therefore, adequate provision for backup support services should exist.

4.2.4.3 Equipment--

All equipment should be evaluated prior to use for its applicability to the HERL project. The relationships of all measurement methods and the variables to be monitored should be well characterized and documented before being approved for use. Similarly, the design and performance of equipment should be thoroughly evaluated with the aid of a professional who has both a theoretical and a practical understanding of the specific instrument operation. In some cases, such as for atmospheric analyzers, comparative studies of different manufacturers' equipment have been conducted by EPA or its contractors. These data should be taken into consideration in establishing precision and accuracy requirements for the project. Definitive statements about the performance of different manufacturers' equipment cannot be based reliably on examinations of single pieces from each manufacturer. Acceptance testing for new equipment should be performed on an item-by-item basis and documented for comparison with future testing. All testing programs should be designed to determine the optimum operating range of the equip-

ment. Equipment performance should be evaluated periodically by systems and performance audits.

To ensure consistently high data quality in the HERL program, a plan for routine inspection and preventive maintenance project management should be developed and followed for all equipment. Scheduling of a particular preventive maintenance program should be based on the identification of critical components that are most likely to fail and the overall effect of equipment failure on data quality.

All maintenance activities should be performed by suitably qualified technical personnel using accepted, documented procedures according to the preventive maintenance plan. The desirability of full- or part-time equipment operator and/or maintenance support should be considered. Frequently, sophisticated instrumentation performs poorly or not at all when many occasional users have access to it. On the other hand, minor but frequent maintenance often keeps an instrument operating at peak performance. In such cases, the cost of a full-time, dedicated operator may be justified.

Documentation of all scheduled and unscheduled maintenance is essential to monitoring and documenting data quality. Permanent records of the maintenance histories of all equipment, including detailed descriptions of all adjustments made, parts replaced, etc., should be kept in individual bound notebooks, dated, and signed by the proper authority.

4.2.4.4 Supplies--

A well-documented acceptance testing program for all incoming expendable supplies should be adhered to. This acceptance screening ensures that supplies not meeting project specifications are not used. The results of a successful acceptance test confirm: (1) that the substance fully corresponds to the manufacturer's specifications and (2) that known or suspected interferences are absent. Acceptance screening under the HERL QA Program involves two classes of consumables: chemicals and biological materials.

4.2.4.4.1 Chemicals--The screening of chemicals or reagent commodities involves verification of assay and examination for impurities. Such screening should be performed on a batch basis using accepted, documented analytical methods. For example, it is necessary to characterize all incoming cylinder gases containing pollutants as to the pollutant concentration and

the composition of the diluent gas(es). Following successful completion of the acceptance test, an expiration date should be permanently marked on each container; containers should be stored on a first-in first-out basis. Permanent labels should be attached to the container with the following information:

Date received: _____
Date tested: _____
Expiration date: _____

Storage conditions that will protect the integrity of the material and protect personnel from harmful exposures should be observed. In particular, parameters such as temperature, light, and humidity should be controlled. Routine recertification should be performed to characterize changes in concentration, formation of new species, or loss of original species to prevent them from degrading project data quality. When possible, the integrity of the substance should be checked prior to each use.

A permanent record of all certification procedures, dated and signed by the appropriate authority, should be kept in a bound laboratory notebook that is filed with the project officer and is accessible to the QA officer.

A central stockroom tracking system should be designed to facilitate rapid reference to the identity of other users of a substance. This is useful for informal sharing of information of interest as well as for rapid identification of users if specific problems (e.g., degradation or contamination) are detected with a particular substance.

Since many chemicals tested at HERL are potentially hazardous to human health, project personnel should be protected from exposure at all times. When chemicals are known to be toxic, mutagenic, carcinogenic, or teratogenic, the project officer should identify where personnel health and safety problems may arise during the performance of the project. Task personnel should be advised of the specific hazards and of proper handling procedures for all potentially hazardous chemicals.²⁸

4.2.4.4.2 Biological materials--To evaluate the possible health hazards associated with environmental pollutants, HERL has taken the approach of using both in vitro and in vivo bioassays in a battery of tests, each test measuring a different endpoint.²⁹ These tests include in vitro microbial and tissue culture assays, in vivo whole organism testing, and human studies. Endpoints measured include mutagenicity, toxicity, carcinogenicity, genetic damage in chromosomes (both somatic and genetic), neurological damage, and related health effects. In vitro tests are cost- and time-effective and can identify substances that may then be screened further for possible health effects in more time-consuming and costly in vivo whole animal testing and human studies. All of these systems present special problems, since biological systems inherently possess a high degree of variation. Because of this inherent variation, quality assurance in this area of research is in the developmental stage.

4.2.4.4.3 In vitro testing--In vitro bioassay testing is an important area of health effects research at HERL; however, several problems have emerged concerning the evaluation of data quality for such testing.³⁰ Estimates of accuracy often cannot be obtained because of the serious lack of standard reference materials for these test systems. Estimates of precision, however, can be obtained by taking replicate measurements. A specific need also exists for the use of standard protocols including guidelines for use of controls and number of replicates. Documentation of all procedures must be an integral part of a bioassay QA program.

In vitro microbial strains and cell culture lines that have been quite thoroughly characterized are available for research purposes. The American Type Culture Collection, 12301 Parklawn Drive, Rockville, Maryland 20852, provides:

- Certified animal cell lines (and is a depository for new animal cell lines)
- Animal viruses and antisera
- Chlamydiae
- Rickettsiae
- Certified pathogenic bacteria

In addition, the following cultures may be obtained from specific research laboratories:

- Ames/Salmonella reverse mutation assay
Dr. Bruce Ames
Department of Biochemistry
University of California at Berkeley
Berkeley, CA 94720
- E. coli/pol A DNA damage assay
Dr. Herbert Rozenkrantz
Department of Microbiology
NY Medical College
Valhalla, NY 10595
- Mouse lymphoma mammalian cell culture forward mutation assay
Dr. Donald Clive
Burroughs Wellcome
Research Triangle Park, NC 27709
- Chinese Hamster Ovary (CHO) Cells forward mutation assay CHO/HGPRT
Dr. Abe Hsie
Oak Ridge National Laboratory
P.O. Box Y
Oak Ridge, TN 37830
- CHO/V79-cell transformation and forward mutation assay
Dr. Elie Huberman
Oak Ridge National Laboratory
P.O. Box Y
Oak Ridge, TN 37830

4.2.4.4.4 In vivo whole animal testing--A large portion of HERL testing involves experimentation with animal subjects. Inbred animal strains have been quite well characterized for generations and correlate closely with certain aspects of human health. For example, C₃H/HeJ mice have been selected for their ability to convert polycyclic aromatic hydrocarbons to their active carcinogenic form.³¹

Specific screening procedures for intramural HERL animal studies should be developed with the assistance of the HERL Laboratory Animal Staff (LAS). Adherence to accepted animal handling procedures and animal facility accreditation by the American Association for Accreditation of Laboratory Animal Care (AAALAC) are considered minimum requirements for all HERL animal studies. Animal selection should be based on awareness of the animal strain's genetically determined immunities, as well as the specific dose-response relationship

to be investigated. The research protocol should clearly state the basis for selection of a particular species and strain. Acceptance testing, or prescreening and surveillance, should be sufficiently comprehensive to ensure that only suitable animals are used as experimental subjects and controls. Although the added expense of such testing may limit the quantity of animals used, the improved data quality will generally more than compensate for this loss.

Comprehensive HERL guidelines for research involving animals are available from the HERL Animal Care Coordinator. In addition, the animal care support facility has a QA Project Plan³² on file with the QA officer. Where appropriate, this plan should be included by reference in the division, branch, and section QA Project Plans and in individual research protocols.

4.2.4.4.5 Human studies--Human subject studies may be the most costly, time consuming, and difficult studies to conduct because of the variability in the human population and because of health and safety requirements restricting experimental exposure levels. However, they may be the most important types of experiments to perform when acquired data will be used in regulatory actions establishing maximum permissible exposure levels for specific pollutants potentially harmful to human health. Variability among human subjects can be minimized, but not eliminated, by careful pretest screening to determine medical history, work history, personal habits, and present health status. Project officers supervising research involving human subjects must be careful to comply with all existing regulations and guidelines for the protection of human subjects.³³

4.2.5 QA Objectives for Measurement Data

Agency policy clearly mandates that all environmentally related data produced by or for the Agency be of estimated quality and emphasizes the importance of employing uniform data quality terminology throughout the Agency. A primary objective of this policy is the establishment of appropriate data quality acceptance criteria for Agency environmental measurement programs. Acceptance criteria are most reasonably derived from considerations of a measurement system's capabilities and/or from the end uses of the data, or from study objectives; they are usually defined in terms of bias, precision,

and completeness and may also involve representativeness and comparability. In addition, resource limitations must often be factored into decisions regarding data quality acceptance criteria.

For each major measurement method employed in a project, the QA objectives for precision, bias, and completeness, as well as the experimental conditions and reference for the method, should be summarized in the QA Project Plan as shown in Table 4-1. Obtaining accuracy estimates for research or state-of-the-art measurement methods may prove difficult or impossible depending on the availability of appropriate reference materials or other accepted methods of making the same measurements. Research projects employing such measurement methods must rely more on peer review and on thorough documentation of procedures as a means of ensuring acceptable data quality. In these cases, it is sufficient to note on the summary table (Table 4-1) that the item is not applicable and explain briefly.

Some of the more important issues that should be considered in assessing data quality parameters and acceptance criteria are summarized below.

Accuracy, bias and precision in the one-sample case

There are typically many sources of variation or error in a measurement process. In the fashion of analysis of variance, the total sum of squares of errors can usually be decomposed into constituent sums of squares representing individual sources of variation. Most numeric measures of data quality relate to some variance component.

The most frequently used measures of data quality are bias, precision, and accuracy. Bias is systematic error; precision measures the closeness of data values to each other; accuracy measures closeness of the experimental values to the target value. Accuracy and precision may be stated as bias and precision.

More specifically, let $y_1, y_2, \dots, y_n$ be a sample of measurements aimed at estimating the target value t , and let $\bar{y}$ denote the sample average $(y_1 + \dots + y_n)/n$. Then,

(1) Average bias = $\bar{y} - t$,

(2) Imprecision = sample standard deviation(s) = $\sqrt{\frac{1}{n-1} \sum_{i=1}^n (y_i - \bar{y})^2}$,

and

TABLE 4-1. FORMAT FOR SUMMARIZING PRECISION, ACCURACY, AND COMPLETENESS OBJECTIVES^a

Measurement parameter (method)	Reference	Experimental conditions	Imprecision ^a Std. Dev.	Bias ^a	Completeness
Examples:					
NO ₂ (Chemiluminescent)	EPA 650/4-75-011 February 1975	Atmospheric samples spiked with NO ₂ as needed	<±10% relative	±5% relative	90%
SO ₂ (24 h) (Pararosaniline)	EPA 650/4-74-027 December 1973	Synthetic atmosphere	<±20% relative	±15% relative	90%

^aImprecision and bias should be clearly defined, including formulas.

$$(3) \text{ Mean squared error} = \frac{1}{n} \sum_{i=1}^n (y_i - t)^2 .$$

Note that

$$(4) \text{ Mean squared error} = \left(\frac{n-1}{n}\right) \text{ imprecision}^2 + \text{bias}^2 .$$

For large samples,

$$(5) \text{ Mean squared error} \cong \text{imprecision}^2 + \text{bias}^2 .$$

The definitions of bias and imprecision are extended to regression situations in the discussion of calibration (Section 4.2.8.3).

Interlaboratory variation (reproducibility) and intralaboratory variation (repeatability, replicability)

As noted above, there are typically numerous sources of variation in a measurement (sampling/analysis) process. Interlaboratory variation (imprecision) is often called reproducibility. This is the variation (standard deviation) among results of measurements on the same sample by different laboratories and, presumably, different analysts.

Two types of interlaboratory variation are often distinguished. Repeatability reflects the variation (standard deviation) among results of measurements of the same sample at different times in the same laboratory. Replicability expresses the variation (standard deviation) among results of independent analyses of the same sample by the same analyst at essentially the same time under the same conditions. Note that $\sigma(\text{reproducibility}) \geq \sigma(\text{repeatability}) \geq \sigma(\text{replicability})$.

It is possible that a precision measure depends on the true level or some proxy for it, such as average apparent level.

In setting criteria for judging performance, such as warning limits on control charts (see Section 4.2.12.1.9), the proper measure of precision must be used. Otherwise, the criteria may be too restrictive, resulting in excessive data invalidation, or not restrictive enough, allowing data of questionable quality to pass through undetected.

Criteria for results from an intralaboratory study involving several analysts and sets of equipment would appropriately be based on the repeatability measure of precision. Likewise, an interlaboratory study should be evaluated against criteria based on the reproducibility measure of imprecision.

- Completeness

Completeness refers to the percentage of planned measurements that are actually taken and appear in the data base. This is related to the statistical problem of missing data. Many data bases contain a vector of variables for each observation, creating the possibility of partially missing data for some observations. For such data sets, a thorough treatment of completeness issues leads to investigations of patterns related to missing data, e.g., identification of population subsets inclined to have missing data, and search for patterns or associations between missing data on two or more variables.

- Representativeness

Measurement processes often involve distinct sampling and analysis phases. Each phase makes its own contribution to bias and imprecision. The term representative is reserved for sampling procedures. The representativeness of a sampling procedure may be gauged in terms of the bias and imprecision attributable to the sampling procedure relative to the total population. As with any attempt to measure data quality, it is necessary to first define the reference or target population unambiguously.

The question of representativeness is as important for basic health effects research activities as for routine monitoring programs; however, because of the inherent variability of biological systems it often presents special problems. Establishing acceptance criteria for representativeness in health effects research areas will, therefore, require close cooperation between QA and technical personnel on a project-by-project basis.

- Comparability

To a great extent, the issue of comparability is one of correlation between the results of applying two (or more) different methods to the same materials. If the paired results cluster tightly about some monotonic smooth curve, then the information content of the two methods is similar; either measurement can essentially be obtained from the other.

If known reference materials are available, then both methods can be applied to them and compared with respect to biases, as well as precisions, in predicting true values from measured values. It is actually possible to estimate the ratio of these precisions (each precision being in units of the "correct value") without recourse to reference standards and the individual calibration curves for the two methods. This can be done by applying both measurement methods to the same set of unknown materials, replicating each measurement, and using the proper statistical analysis.

An issue of particular importance to health effects research that is raised by comparability is that of the use of concurrent controls. Controls do not necessarily legitimize interstudy comparisons. However, the comparison of two studies is much more credible if both studies include control subjects. The comparison of the studies can then be attempted relative to their controls; or, if controls respond sufficiently similarly, then some justification of direct comparison of experimental subjects is obtained. Even with controls, rather strong assumptions are required for comparison of studies conducted at different institutions.

4.2.6 Sample Collection

Collection of a representative sample is of paramount importance to any measurement process. No amount of analytical expertise or data manipulation will result in meaningful project conclusions if the samples being analyzed are not representative of the parent material or population under study.

Collecting a suitably representative sample may be the most technically difficult, hazardous, and time-consuming part of the measurement task, and the one that is most often overlooked. The assumption that a sample retains the desired property of the system from which it was extracted deserves close examination. Sampling may range from collecting a representative volume of aerosol from an exposure chamber to obtaining tissue samples from rats or biological samples from human subjects. In some cases, additional environmental data may be required (e.g., temperature, pressure, time of day) to document the collection procedure. In many health effects research systems, separate control samples must also be obtained.

The overall objectives of a research project affect many aspects of sampling. Factors that must be considered in meeting project objectives include:

- Resource limitations
- Complexity of measuring the parameters of interest
- Duration of the study
- End use of the data
- Number of samples to be collected
- Sampling frequency
- Type of samples

For each major measurement parameter being examined in a research project, a detailed description of sampling procedures should be provided and, where applicable, all of the topics in the following subsections should be addressed. In addition, responsibility for all sampling should be clearly delineated and approved by the project officer.

4.2.6.1 Sample Site Selection--

The selection of the sampling site is critical to obtaining representative data, whether the project involves environmental monitoring of air or water pollution parameters at specific sites or the monitoring of physiological or morphological changes in a specific target organ or tissue sample from an animal exposed to an environmental contaminant. A description of the criteria used to select the sampling sites should be given for each project.

4.2.6.2 Sampling Procedures--

Various EPA-approved or other standard sampling methods are available for a wide variety of sampling needs; these should be reviewed at the outset of any project to ascertain if they can be used directly or with modifications. Use of EPA-approved methods or other standard sampling methods is required where applicable. Where existing EPA-approved or standard methodology is not applicable to a particular project, sampling procedures may be obtained from the scientific literature, or new methods may have to be developed. In all cases, the sampling procedures used should be written as standard operating procedures (SOPs) and included in full or by reference in the QA Project Plan and research protocol. All SOPs should be written in enough detail so that the sampling procedures can be duplicated by another technically qualified individual. In cases where modifications of SOPs are employed, the modifications may be documented either by reference to the SOP with appropriate modifications noted or by issuance of a new SOP with modifications incorporated. The choice should be dictated by the extent to which the method will be used.

After a sampling procedure has been selected and suitably modified for a particular research project, additional details related to the sampling program for the project need to be identified. These include sampling

frequency, number of samples, size of samples, and specific timing of sample collection with respect to natural circadian, annual, or seasonal cycles.

4.2.6.3 Sampling Flow Diagrams, Charts, or Tables--

Since sampling often involves a specific sequence of activities, flow diagrams illustrating sampling sites, key personnel, sampling methods, dates of collection, maximum sample holding times, and other pertinent information may be useful (Figure 4-7).³⁴ Charts identifying site locations may also provide easily accessible information and tables may provide a complete listing of reagents, collection containers, or accessory supplies that the sampling effort will utilize.

4.2.6.4 Sample Storage and Handling--

If analysis cannot be performed during or immediately after collection, the sample must be handled and stored in an appropriate manner to maintain its integrity. Handling and storage procedures assume varying importance depending on the nature of the sample; however, in many cases there is a finite residence time that can reasonably ensure that the sample is not modified (or at least modified in a known way, for which correction can be made). Proper storage conditions for all samples must be provided before, during, and after analysis.

All procedures employed for ensuring the integrity of the sample should be completely documented, and criteria for rejecting inadequate, inappropriate, or degraded samples should be clearly defined. Key project personnel responsible for ensuring, evaluating, and documenting sample integrity should be clearly identified in relation to overall project management and to sample custody authority.

The following factors must be considered in preventing degradation, contamination, or loss of a sample.

4.2.6.4.1 Container material--The suitability of the selected container material for maintaining sample integrity may be ascertained by using blanks or known concentration samples under worst-case storage conditions. Once a suitable container material has been identified, the manufacturer, item, and lot number should be documented and the container material should be used for all samples for the duration of the study. Where samples must be shipped

SAMPLE FOR BIOLOGICAL ANALYSIS

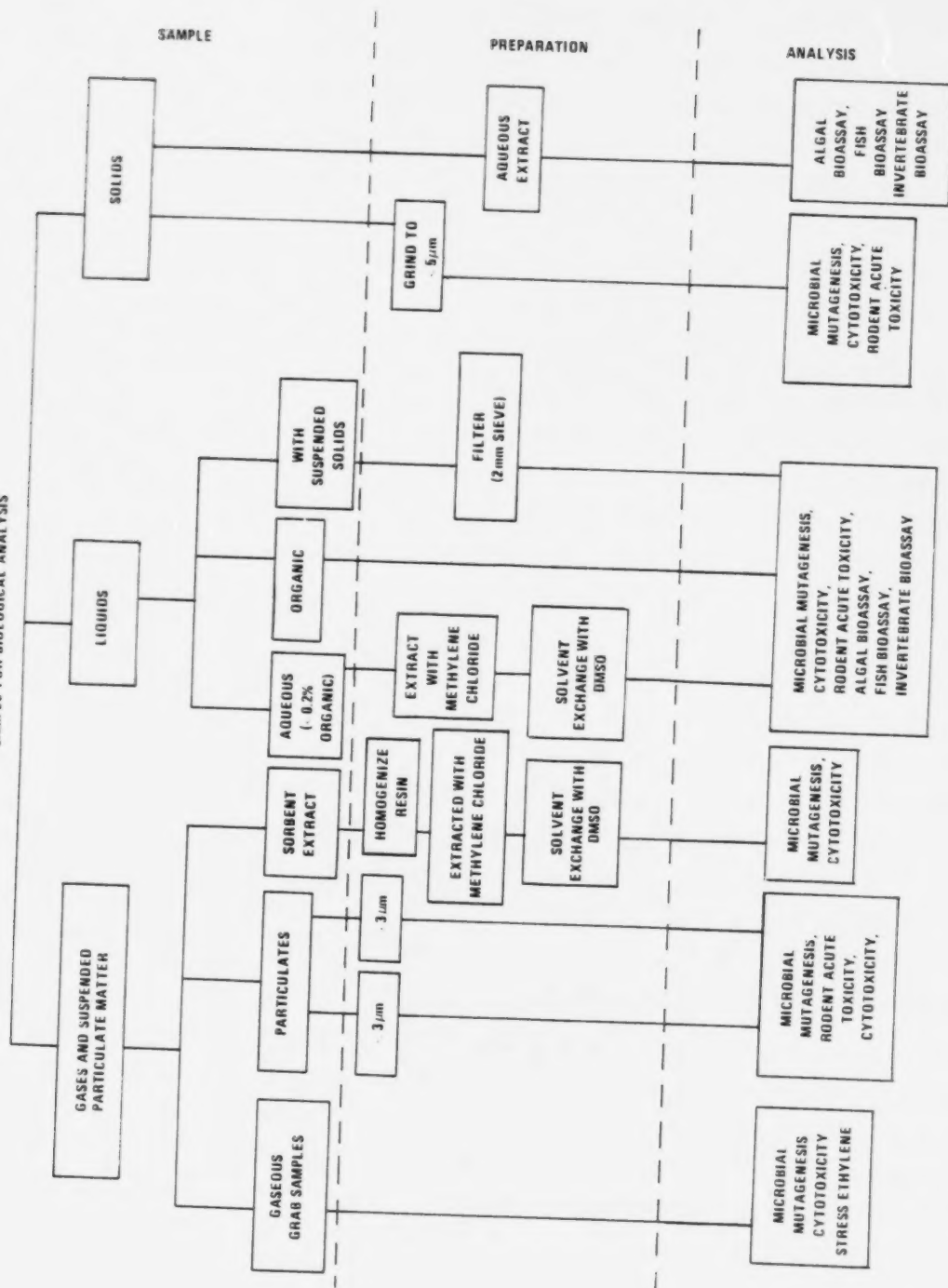


Figure 4-7. Sample flow diagram for sample collection and analysis. 34

or transported, container material should also be of a quality to prevent breakage during shipment.

4.2.6.4.2 Sample identification--All samples should be uniquely identified with individual labels for each sample container. The label information should be adequate for tracing an archived sample back to its original sampling site without ambiguity. Improper identification of samples will result in irretrievable loss of data from the project.

4.2.6.4.3 Environmental conditions--The environment in which a sample is stored, transported, or archived is of primary concern in maintaining sample integrity. Proper environmental conditions (e.g., temperature, pressure, light level, relative humidity, and agitation) should be determined and specified for each sample type in every measurement project.

4.2.6.4.4 Reagents--When chemical reagents are added to a sample as part of the collection, preservation, or storage procedures, checks on reagent quality should be performed and documented to identify possible contamination (see Sections 4.2.4.4 and 4.2.12).

4.2.6.5 Recordkeeping--

Where appropriate, standard format data sheets for sample collection should be designed at the outset of a project and used for the duration of the project. These data sheets should provide space for a unique sample identification number, date of collection, collector's signature, project number, and comments about sampling conditions related to sample quality. When bound, these sheets may serve as the sampling logbook. When use of standard format data sheets is not appropriate, all sampling data should be recorded chronologically in a clear and complete manner in a single logbook. In all cases, accurate recordkeeping should be emphasized for all project personnel. For a complete discussion of recordkeeping, refer to Section 4.2.10.

4.2.7 Sample Custody

All projects involving health effects research should document and implement a chain of possession and custody of any sample collected, whether or not the resulting data are to be used in enforcement cases. Such proce-

dures ensure that the samples are collected, transferred, stored, analyzed, and disposed of only by authorized personnel.

4.2.7.1 Field Custody Procedures--

The following sample custody procedures are specifically applicable to large-scale monitoring programs involving shipment of samples from the sampling site to the analysis laboratory.³⁵ They are intended to be comprehensive and may be used as guidelines for all measurement or research programs. Depending on the specific scope and nature of a project, the project officer should tailor the sample custody procedure to individual project requirements. The most important concern is that the sample custody procedure be properly documented and adhered to for the duration of the task.

1. Samples must be accompanied by a chain-of-custody record that includes the project title, collectors' signatures, collection site, date, time, type of sample, sequence number, number of containers, and analyses required. (An example of a chain-of-custody record is shown in Figure 4-8. Note: Standardized chain-of-custody formats should be tailored specifically to each project and used consistently for the duration of the project.) When transferring possession of samples, the transferor and transferee sign, date, and time the record sheet. This record sheet allows transfer of custody of a group of samples from a collection area to the central analysis laboratory. When a custodian transfers a portion of the samples identified on the sheet to the laboratory, the individual samples must be noted in the column with the signature of the person relinquishing the samples. The laboratory person receiving the samples acknowledges receipt by signing in the appropriate column.
2. The collector custodian has the responsibility of packaging and dispatching samples to the laboratory for analysis. The dispatch portion of the chain-of-custody record must be filled out, dated, and signed.
3. To avoid breakage, samples should be carefully packed in shipping containers such as ice chests. The shipping containers are padlocked for shipment to the receiving laboratory. Special shipping precautions are necessary for toxic or hazardous materials and must conform to Federal regulations.³⁶⁻³⁹
4. Packages must be accompanied by the chain-of-custody record showing identification of the contents. The original record must accompany the shipment. A completed copy is retained by the project officer after completion of the analysis.

CHAIN OF CUSTODY RECORD

[illegible]

Figure 4-8. Sample chain-of-custody record.³⁵

5. If sent by mail, register the package with return receipt requested. If sent by common carrier, a Government bill of lading should be obtained. Receipts from post offices and bills of lading should be retained as part of the permanent chain-of-custody documentation.
6. If delivered to the laboratory when appropriate personnel are not there to receive them, the samples must be locked in a designated area within the laboratory so that no one can tamper with them, or they must be placed in a secure area. The recipient must return to the laboratory, unlock the samples, and deliver them to the appropriate custodian.

4.2.7.2 Laboratory Custody Procedures--

Suitable laboratory sample custody procedures include the following:³⁵

1. The laboratory should designate a sample custodian and an alternate custodian to act in his/her absence. In addition, the laboratory should set aside a sample storage security area. This should be a clean, dry, isolated room with sufficient refrigerator space that can be securely locked from the outside.
2. Samples should be handled by the minimum possible number of persons.
3. Incoming samples should be received only by the custodian, who will indicate receipt by signing the chain-of-custody record sheet accompanying the samples and retaining the sheet as a permanent record. Couriers picking up samples at the airport or post office shall sign jointly with the laboratory custodian.
4. Immediately upon receipt, the custodian places the samples in the sample room, which will be locked at all times except when samples are removed or replaced by the custodian. Only the custodian should have access to the sample storage room.
5. The custodian should ensure that all samples are properly stored and maintained under appropriate environmental conditions (i.e., temperature, humidity, light intensity).
6. Only the custodian should distribute samples to task personnel who are to perform analyses.
7. In the laboratory notebook or analytical worksheet, the analyst records information describing the sample, the procedures performed, and the results of the analysis. The notes should be dated, should indicate who performed the tests, and should include any abnormalities that occurred during the testing procedure. The notes should be retained as a permanent record in the laboratory. In the event that the person who performed the tests is not avail-

able as a witness at the time of a trial, the Government may be able to introduce the notes in evidence under the Federal Business Records Act.

8. Approved methods of laboratory analyses should be used and documented on all samples.
9. Laboratory personnel are responsible for the care and custody of a sample once it is handed to them and should be prepared to testify that the sample was in their possession and view or secured in the laboratory at all times from the moment it was received from the custodian until the analyses were completed.
10. The laboratory area should be maintained as a secured area and should be restricted to use by authorized personnel only.
11. Once the sample analyses are completed, the unused portion of the sample, together with identifying labels and other documentation, should be returned to the custodian. The returned, tagged sample should be retained in the custody room until permission to destroy the sample is received by the custodian.
12. Samples should be destroyed only upon the order of the project officer in consultation with the QA officer and only if it is certain that the sample is no longer required. The same destruction procedure is true for tags and laboratory records.

4.2.7.3 Evidentiary Considerations--

As accurate and reliable environmentally related measurements become increasingly important in documentation of environmental conditions of public health concern, organizations collecting these data must address evidentiary considerations.

Recording all sample custody procedures and promulgated analytical procedures in writing will facilitate the admission of evidence under Rule 803(6) of the Federal Rules of Evidence (Public Law 93-575). Under this statute, written records of regularly conducted business activities may be introduced into evidence as an exception to the hearsay rule without the testimony of the person(s) who made the record. Although it would be preferable, it is not always possible for the individuals who collected, kept, and analyzed samples to testify in court. In addition, if the opposing party does not intend to contest the integrity of the sample or testing evidence, admission under Rule 803(6) can save a great deal of trial time. For these reasons, it is important that the procedures followed in the

collection and analyses of evidentiary samples be standardized, formally documented as written SOPs, and described in an instruction manual, which, if need be, can be offered as evidence of the regularly conducted business activity followed by the laboratory or office in generating any given record.³⁵

4.2.8 Calibration

Calibration is the process of establishing the relationship between the output of a measurement system and that of a known input; it allows different instruments to be correlated with each other and with a specified reference standard.²⁰ Calibration is an integral part of any measurement process and is a major factor in controlling the accuracy of results. Since the reported accuracy of the measurement method can be no better than the accuracy of the calibration system, calibration is also a limiting factor.

A sound calibration system should include provisions for:

- Selection of the highest quality calibration standard.
- Detailed documentation of calibration procedures as written SOPs including specifications for reagents, materials, support equipment, and pertinent environmental conditions.
- Construction of a calibration curve or a corrective table to determine appropriate correction factors.
- Maintenance of a record of calibration histories for instruments, support equipment, and standards including identification of instruments and standards, dates of calibration, and calibration results.
- Determination of calibration frequency needed to ensure quality data collection.
- Identification of acceptance limits in terms of bias and imprecision, and specification of corrective action to be taken when limits are exceeded.

4.2.8.1 Calibration Standards--

Calibration standards should be of the highest quality available and fully characterized. In the United States, the National Bureau of Standards (NBS) holds the position of final authority in the preparation of many reference materials and the NBS Standard Reference Materials (NBS-SRMs) are generally regarded as the best standards of each type available.

Investigators should check on the availability of NBS-SRMs applicable to their measurement needs. The NBS has been rapidly developing suitable standard reference materials for environmentally related measurements. The NBS provides information on available standards in its regularly revised Special Publication 260,⁴⁰ regular publicity releases, and in a special mailing list for newly issued NBS-SRMs. In addition, a new monthly column in American Laboratory entitled "Reference Materials," edited by the Deputy Chief of the Office of Standard Reference Materials, is an excellent source of current information on NBS-SRMs. Considering the rapidity with which NBS-SRMs are being developed and the pressing need to compare data to standards of known high quality, this column should be reviewed regularly by each investigator. Examples of currently available NBS-SRMs that may be applicable to environmental measurement systems include:

- Hydrocarbon Blends
- Primary Working and Secondary Standard Chemicals
- Microchemical Standards
- Metallo-Organic Compounds
- Isotopic Reference Standards
- Radioactivity Standards
- Industrial Hygiene Standards
- Trace Element Standards
- Clinical Laboratory Standards
- Environmental Standards
- Biological Standards
- Certified Physical Properties Standards.

Selected examples of some of these NBS-SRMs are shown in Appendix A.

Use of NBS-SRMs completely fulfills the requirement of high quality and full characterization. However, because NBS-SRMs are not mass produced and are individually characterized by lot, they are expensive and often in short supply. Therefore, it is generally desirable to employ secondary standards

as the actual calibration standards, maintaining an NBS-SRM as a final high quality calibration standard for the secondary working calibration standard. Whenever a secondary standard is employed in a calibration, it is necessary that traceability to a quality primary standard be established and maintained. EPA regulations now require traceability of calibration standards to NBS-SRMs where possible,^{41 42} and it is likely that this requirement will appear in all future regulations.

Unfortunately, for many common measurement processes routinely used at HERL, there are no NBS-SRMs available. In these cases, the investigator must use the best available calibration standard or devise a standard. Such standards must also meet the requirements of high quality and complete characterization applicable to NBS-SRMs. Careful characterization of such standards involves rigorous testing to establish the true value of the reference material within stated limits of imprecision. Such rigorous testing may include repeated analysis of the standard material by more than one analyst or technique or round-robin interlaboratory analyses.

4.2.8.2 Calibration Procedures--

Written procedures describing each step in the calibration process are required and should be prepared as SOPs under documentation control. Calibration procedures may be prepared in-house by qualified personnel, derived from instrument or process manufacturer's instructions, or obtained from sources such as the American Society for Testing and Materials⁴³ or the NBS.⁴⁴ Only the most current and acceptable procedures available for the specific calibration should be used. In addition, only personnel familiar with the measurement process and the calibration procedure should perform the calibration.

An aspect of the calibration operation that is often overlooked is the calibration or certification of reagents, materials, and support equipment. Most calibration procedures use equipment and/or reagents in addition to the standard(s). All such reagents, materials, and support equipment should be subjected to recent calibration or certification prior to use in the standard calibration procedure. Even for authoritative standards, such as NBS-SRMs, sample integrity may be questionable if proper storage and handling procedures are not observed.

Maintenance of environmental conditions should be appropriate to the specific calibration measurement being conducted. Proper environmental conditions must be maintained and documented during the entire calibration procedure. The use and handling of the calibration standard should be of particular concern as potential problems in calibration may arise with mistreatment of otherwise valid calibration standards. Problems associated with the use of some common standards include:

1. Permeation devices should be used and stored under carefully specified environmental conditions of humidity⁴⁵ and temperature⁴⁶ and should be protected from possible environmental contaminants.⁴⁵
2. Certain gases in pressurized cylinders require special procedures for routine installation to prevent cylinder and regulator contamination with atmospheric oxygen or moisture.
3. Electronic standards frequently require periods of several hours for stabilization of output.
4. Most solid standards require conditioning at a specified humidity prior to weighing.

These examples illustrate that users of standards should be familiar with specified environmental conditions pertinent to handling of each standard. It is imperative that this be recognized if high quality data are to be obtained from the measurement process.

4.2.8.3 Analysis of Calibration Data--

For analysis of calibration data, as for any type of data analysis, it is important to completely specify the assumed underlying model and to perform QC (goodness-of-fit) checks of model validity. A detailed discussion of issues related to analysis of calibration data may be found in Reference 47.

The equation

$$y = f(x) + e(x)$$

is often employed for calibration data, where x denotes reference value, y denotes measured value, $f(x)$ is the systematic or bias component of the measurement, and $e(x)$ is a random error term with mean (expectation) zero. The systematic (bias) term $f(x)$ is often assumed to be linear:

$$y = (ax + b) + e(x),$$

where a is the slope and b is the intercept of the line.

A standard regression assumption is that the error variance $\sigma^2(x)$ of $e(x)$ at reference value x is constant, $\sigma^2(x) \equiv C$. This assumption, made primarily for reasons of mathematical convenience, is often violated in practice. Chemical analyses, for instance, often contain an error component proportional to the level of analyte being measured, $\sigma(x) = Ax$. In some cases, the error variance has two components, one affected by the analyte level, the other constant and present at all levels, operating as additive noise, $\sigma^2(x) = Ax^2 + C$.

Coefficient estimates a and b obtained under the equal variance assumption are unbiased ("correct in the long run"; correct for an infinite sample) as long as the systematic component is correctly modeled ($ax + b$). This is the case even if the equal variance assumption fails. On the other hand, coefficients based on the equal variance assumption may be imprecise in the presence of unequal variances. Appreciable gains can result from appropriately modeling variances as functions of targets and using the inverse estimated variances as weights in the regression scheme.⁴⁸ However, Hunter⁴⁷ warns that "as a practical statistical problem, rejecting the hypothesis that σ^2 is constant is not an easy matter; many replicate observations are required and assumptions concerning the distribution of the errors of observation can be crucial."

Ideally, before the process is put into routine use, an in-depth characterization study of the measurement process is conducted to yield enough data for reasonably powerful goodness-of-fit checks of the model. These checks can focus separately on the deterministic (mean) and random components of the model; i.e., on (1) adequacy of the linear model, which can be checked by overfitting within appropriate classes of models, (2) tests for constancy of variance, and (3) investigation of components of variance.

The most important parameters in a (linear) calibration are the bias parameters (slope a and intercept b), and squared imprecision (σ^2). In addition to reporting estimates of these parameters, it is also desirable to report confidence intervals for the bias and imprecision parameters (a , b , σ^2) and to monitor the parameters with control charts²⁰ (Section 4.2.12.1.9).

The formulas for these calculations can be found in most standard statistics texts.^{47 48 49}

It is also desirable to associate a confidence interval for the true value x corresponding to a given measured value y . This problem is incorrectly treated in a number of otherwise reputable references. A proper solution should take into account the uncertainty in y as an estimate of its expectation and the considerations of simultaneous statistical inference.⁴⁷

4.2.8.4 History of Calibration--

Documentation of each calibration must be maintained to establish a complete history of all calibrations performed on a measurement system. Control charts for slope, intercept, and standard error constitute partial graphical histories of results. The history of calibration for a measurement system should include complete documentation of:

- Dates of calibration
- Identification of the standards used
- Support equipment, reagents, and devices used
- Personnel performing calibration
- Pertinent environmental conditions
- Results of calibration (raw data and summary statistics)
- Corrective actions taken.

4.2.8.5 Corrective Action--

To characterize the dynamics of the system, each measurement system should undergo an initial intensive calibration phase in which it is frequently calibrated. The object is to investigate trends (e.g., time trends) in parameters such as slope (a), intercept (b), and the imprecision (σ). Two important uses of this information are: (1) to determine if corrective action (adjustment or replacement of equipment) is necessary; and (2) to schedule future maintenance and calibration.

Exceeding preestablished control limits (see Section 4.2.12.1.9) calls for corrective action, which should be specified by QA personnel. In some cases, these limits follow from an a priori accuracy requirement. In other

cases, they may result from observation of the measurement process over a period of time (e.g., the intensive audit phase). If the measurement process is judged to be satisfactory, then the average parameter estimates (e.g., slope, intercept, imprecision), plus or minus three of their standard errors, may serve as future control limits.

4.2.8.6 Calibration Frequency--

It is possible to study the behavior of a measurement system over time and to define the limits of acceptable performance. It is thus possible to estimate the probability of unacceptable performance during a time interval of arbitrary length between calibrations. The time between successive calibrations can then be chosen as the maximum time for which the probability of exceedance is acceptably low.

In many cases the structure of a QA/QC program is largely determined by practical considerations. For instance, many measurement processes exhibit so much day-to-day variation that some quality control is necessary on a daily basis. On the other hand, the need to accomplish routine project work may largely dictate the QC effort within a day. In some cases mathematical optimization techniques are useful in scheduling QC measurements.

These procedures will not anticipate nonroutine interferences or changes to the measurement system as opposed to trends. Perceptions of operating personnel are the best source for this information and any suspicion that such a change has occurred should be followed by recalibration.

4.2.9 Sample Analysis

4.2.9.1 Selection of the Method of Analysis--

Selection of the method of analysis to be employed on any sample is dictated by three major considerations:

- Project data quality requirements
- Cost and resource limitations
- Use of the resulting data.

Attributes of a measurement method that address data quality requirements and that should be considered in the selection process include:

- Accuracy (correctness)

- Precision (reproducibility)
- Applicability (usable range)
- Specificity (uniqueness of response)
- Reliability (overall dependability)
- Detectability (minimum amount measurable above background)
- Sensitivity (response per unit concentration).²⁰

From a management perspective, the project officer must also consider the type and number of samples to be analyzed in relation to cost considerations including the elapsed time for completion of the analysis, manpower resources, availability of required equipment, cost of materials, and the level of training required of project personnel for completion of the proposed project.²⁰ In all extramural projects, there should be a clear understanding and agreement between the project officer and the extramural organization in these areas.

The ultimate use of the analyzed data is the third consideration in selection of the analytical method. In interlaboratory studies where several research groups are providing data to a common data bank or are cooperating in a joint research project, uniformity of the analytical methodology is particularly important to remove methodology as an experimental variable. For these cases, use of EPA-approved methods or other standardized analytical methods, where applicable, is recommended. Widespread use of an analytical method usually indicates that the method is reliable and therefore tends to support the validity of the reported test results. Conversely, the use of little-known analytical techniques forces the data user to rely on the judgment of the analyst, who must defend his choice of the analytical technique. For much of the health effects research conducted by HERL, however, standard EPA-approved methods are not available and specific analytical methods must be developed for each project.

4.2.9.2 Documentation of Analytical Procedures--

After the measurement method has been selected, a clear, concise description of the analytical procedures should be documented containing sufficient detail so that the method can be repeated by other technically

qualified personnel. These procedures should include a detailed description of appropriate QC activities (see Section 4.2.12). The project officer should choose the QC activities appropriate to a given task that will provide the highest quality data given the existing limitations of the selected analytical methods.

Various EPA-approved or other standard methods are available for a wide variety of analytical needs; these should be reviewed at the outset of any project to ascertain if they can be used directly or with modifications. Use of EPA-approved methods or other standard sampling methods is required where applicable. Where existing EPA-approved or standard methodology is not applicable to a particular project, analytical procedures may be obtained from the scientific literature, or new methods may have to be developed. In all cases, the analytical procedures used should be written as standard operating procedures (SOPs) and included in full or by reference in the QA Project Plan and research protocol. All SOPs should be written in enough detail so that the analytical procedure can be duplicated by another technically qualified individual. In cases where modifications of SOPs are employed, the modifications may be documented either by reference to the SOP with appropriate modifications noted or by issuance of a new SOP with modifications incorporated. The choice should be dictated by the extent to which the method will be used.

4.2.10 Recordkeeping

High quality recordkeeping serves at least two useful functions: (1) it makes possible the detailed reanalysis of a set of data at a future time when the model has changed significantly, thus increasing the cost-effectiveness of the data; and (2) it may be used in support of the experimental conclusions if various aspects of the study are called into question. This latter point is basic to scientific research. It is often possible to interpret data in more than one way, therefore the raw data must be available for evaluation by qualified professionals. When recordkeeping is careless, suspicion is quickly aroused that all other aspects of the research are of similarly poor quality.

The cardinal principle of recordkeeping for scientific research is that all raw data must be retained in a manner that is secure and that expedites validation and access. Complete, permanent, and chronological records of all project activities should be maintained. All information that might be useful in data analysis and interpretation should be recorded. This includes, in addition to raw data, explicit identification of equipment, reagents and other supplies, experimental subjects (e.g., animals), protocol modifications, and QC activities. The exact organization of the project records should be specified in the work plan, research protocol, or QA Project Plan and is subject to approval by the project officer.

A cross-referencing system should be used if the data are to be easily accessible following their initial use. Such a system may be of various levels of complexity, depending on the amount of data collected and their potential applications. Requirements for nonclinical laboratory reports and records and their generation, storage, retrieval, and retention on a long-term basis have been specified in GLP regulations.¹⁸ When data are logged by computers, it is important that adequate provision be made for redundant and physically separate long-term storage of such records (Section 4.2.11.2).

All technical personnel should be provided with a personal notebook in which they chronologically record all data and pertinent observations in dark permanent ink. Where possible, formats for data should be standardized for the project and not left to individual discretion. Where a large number of measurements are made repeatedly, the use of preprinted standard format data sheets is strongly recommended. When bound, these sheets often serve most usefully as the laboratory notebook. The project officer should check that the standard format data sheets have been designed to ensure complete data, high productivity of technical personnel, and ease of reading the raw data. Data coding forms should be designed in consultation with personnel who must record and evaluate the data. In some cases, a data transfer can be avoided by designing forms in consultation with keypunchers or other data entry personnel. Information should be preprinted on forms when possible. This applies to column headings, variable names, or questions on questionnaires. In some cases it is possible to code multiple observations with the same format on a coding sheet. Variables that identify the coding form need

not be repeated on each observation, although it may be desirable to include them on each observation when the data are computerized.

Efforts should be made to encourage the entry, not only of specific data (e.g., weights, absorbances, volumes, atmospheric or meteorological conditions, and status of instruments), but also of anecdotal data and comments. Erroneous or invalidated data should be indicated in such a way that the entry is flagged, but remains legible. Drawing a single line through the entry, so that the value is still readable, is an acceptable indication; this flag should be initialed and the reason for suspicion of the datum should be recorded in the comments column. Such information may become extremely valuable in subsequent evaluation of a completed experiment or in initial planning of a related one.

It may be advisable to provide station, laboratory, or task data notebooks, in addition to individual notebooks or project data notebooks, to follow the relationship among various project activities. Such records will generally take the same form and adhere to the same recommendations as personal notebooks. Related notebooks should be cross-referenced.

Instrument logbooks should be provided in which to record all data relating to a particular piece of equipment. This log maintains, in one location, a chronological record of instrument operation, calibration, maintenance, failures, and idiosyncrasies. Such a record is often useful in determining operational trends, spare parts inventories, etc. A specific format should be used for recording such data to minimize the possibility of omission of important procedures or data.

Computerized data acquisition systems have many advantages, but require close monitoring and frequent auditing for erroneous or stray electrical signals. Many systems are able to concurrently produce printed output as well as computer-readable output (usually magnetic tape); where possible, it is advisable to employ both.

4.2.11 Data Management

Data management operations include collection, storage, backup, validation, transfer, reduction, analysis, interpretation, and reporting. Each of these aspects of the data analysis/processing regime must be addressed in

the research protocol or the QA Project Plan, together with associated QA measures and their documentation.

4.2.11.1 Data Collection--

A clear description of the manner in which raw data are collected is essential to QA planning. These data, representing the actual measured values in chronological sequence, subsequently may be flagged as invalid but must never be destroyed or deleted. Manually collected data are frequently monitored by the person recording the data. However, computerized data acquisition systems do not have the potential for this treatment and are known to pick up false voltage transmissions, which may introduce error.

Analysis of data trends and of the relationships between various parameters may be used to establish windows or intervals within which valid data are expected to occur, leading to the application of control charts or cumulative sums charts for real-time and on-line data validation.^{50 51} It must be recognized, however, that evaluating data to determine if they lie in an expected range does not alone constitute adequate validation. Clearly, data can remain in such an interval but still involve considerable error.

In all cases, methods for assessing the validity of the recorded raw data must be established prior to project initiation and documented in the QA Project Plan (see Section 4.2.11.4). It is a QA function to evaluate the adequacy of these methods with respect to time, place, and documentation.

4.2.11.2 Data Storage and Backup--

Raw data must be stored in such a way that they are not degraded or compromised and that any datum (value) desired may be retrieved (uniquely identified). For computerized raw data, there must always be at least one copy that is off-line and not machine-mounted. It is a common practice of large computation centers to provide this service with regularly scheduled backups for users renting on-line disk space. The users should know when such backups are performed and how many prior versions are retained. A project may provide heightened security by supplementing these backup measures with further backup stored in separate locations. Duplication of user-owned tapes is usually the responsibility of the user.

Raw task data must be securely archived. Such aspects as storage media (e.g., paper, punched cards, paper tape, magnetic tape, or disk), conditions, and location must be addressed. Access by authorized personnel and retention time must also be addressed in the research protocol or the QA Project Plan. For certain types of studies, EPA's proposed GLPs¹³ are quite explicit.

The storage media, conditions, and locations should be selected based on project-specific criteria. Computer files (tape or disk) should be "exercised" due to their rather high instability. Physically separate storage of duplicate raw data sets should be considered. The retention time will vary, according to project objectives and legal considerations, but it should be stated clearly at the outset of any study.

Access to the archived data should be described. The fewer persons allowed access, the less chance there is of losing the data. This may conflict with the need to disseminate data to a wide audience. In such a case, copies of data may be provided rather than permitting free access to the unrecoverable raw data.

Another aspect of data storage that should be addressed is data inviolability. Raw data must never be altered. If an error in data can be demonstrated and the correct value(s) determined, then of course the data should be corrected. However, such changes must be documented fully, including date and reason for correction. If records are kept in laboratory notebooks, then drawing a single line through the incorrect value and writing the correct value next to it, in such a way that both entries are legible, is permissible. The date, reason for change, and identification of the individual making the change must be recorded. For computerized data files, it is advisable to keep a separate file containing notes fully documenting data changes. This level of security is unnecessary for the correction of key-punch, encoding, and transcription errors.

These documentation standards also apply to any outlier detection and dispensation procedures that may be employed. It is advisable to keep a variable on the master file to indicate whether an observation is normal, an outlier, or aberrant for some other reason.

It is not necessary that all data sets created from the raw data set be saved or backed up. In fact, if a second or later generation data set is

retained without sufficient documentation to explain how it was created, then that data set can be of little or no value for QA purposes. Thus, more important than retention of intermediate data sets or analyses is the adequate documentation of the procedures used. All computer code (including job control language) that accomplishes objectives planned in the protocol or results to be cited in the final report should be saved and dated. Documentation must permit reconstruction of analyzed data sets and analysis computer programs.

4.2.11.3 Data Transfers--

Data transfer changes the form or location of a data set, but not its content. Thus, a transferred data set may be used to fully reconstruct its originating data set. If data transfer is error free, then no information is lost in the transfer and the input is completely recoverable from the output. Examples of data transfer are copying the raw data from the notebook onto a data form for keypunching, converting a written data set to punched cards, or copying from a computer tape to disk.

An audit trail should be kept as a check on the correctness of data transfer operations. An audit trail is an account of the data (values, pages, keypunch forms, keypunch cards, etc.) and a verification after each operation on the data that the number of data items fed into the process is reliably reflected by (usually equal to) the number of data items resulting from the process. An audit trail provides a necessary, but not sufficient, check on the accuracy of data transfers.

A good general rule is to minimize the number of data transfer steps in the data processing, since the overall probability for errors increases with the number of such transfers. Often this can be influenced by judicious design or choice of data forms. For instance, since the reliability of keypunchers and other data entry personnel is highly dependent upon the form and legibility of the data they receive, it is highly desirable to initially record the raw data on the same form used for data entry (keypunching) or in computer-readable form. Data entry personnel should be consulted in advance and, insofar as possible, forms should be designed to accommodate them; standardized 80-column Fortran coding forms (6X28-7327-6 IBM) are often desirable.

As part of the study design, an overall admissible transfer error rate should be specified. One of the primary purposes of data validation is to test whether this error rate has been exceeded by comparing the analysis data set with raw data. If the transfer process has several components, their individual error rates are not of particular concern, as long as the composite error rate is below the desired level.

4.2.11.4 Data Validation--

Data validation has been defined by EPA as ". . . the process whereby data are filtered and accepted or rejected based on a set of criteria."⁴⁶ This process may include manual or computerized checks and clearly involves specified criteria. The research protocol or QA Project Plan should state clearly that raw data are not to be altered, and study documentation should indicate how subsequent data sets are generated and validated.

Validation checks may include evaluation of the data with respect to physically determined criteria (e.g., a record indicating a negative weight is not reasonable). Similarly, as the sophistication of the model increases, relational checks between measured parameters may also be used.

The data sets to be statistically analyzed should be compared with the first recorded form of the data to estimate the error rate. The QA officer may request samples from both the raw data and the analysis data set. QA functions involve definition of error and specification of allowable error rates. In the case of a small data set, QC checks may consist of item-by-item verification that the error rate does not exceed the allowable limit. For large data sets, data validation should be considered as a hypothesis-testing problem, with type I and II error probabilities⁴⁹⁻⁵² chosen by appropriate QA personnel. A random sample of a size sufficient to achieve the desired significance level and power should be drawn. Dodge-Romig tables may be employed to determine sample size, if 90 percent power is acceptable.⁵³ This subsample is then compared item by item with the corresponding raw data to determine if the error rate is acceptable. QA requirements may include documentation in the form of a printed copy of the subsample and access to the raw data.

4.2.11.5 Data Reduction--

Data reduction includes all processes that transform one data set to another in such a way that the original data set cannot be recovered from the reduced data set. It is distinct from data transfer in that it entails a reduction in the size (or dimensionality) of the data set and an associated loss of information. Assumptions about the distribution of the observations are implicit in data reduction, making it a data analysis activity. For instance, if repeated measurements of a quantity are made in the laboratory and summarized as a mean and standard deviation, then statistical theory can be invoked to justify the sufficiency of these two measurements, if the data follow a normal distribution.

If the data are reduced before analysis, the study documentation or data management analysis scheme must clearly define the mathematical or other processes used to obtain the reduced data set from the raw data set. Quality assurance should address the accuracy of the mathematical operations used in the reduction process. Permanent data reduction, resulting in irretrievable loss of raw data, should be avoided if at all possible. However, in some instances, the sheer volume of data that would result makes it impractical to save each datum. In such cases data subgroups are sometimes summarized by statistics such as averages, standard deviations, and sample sizes. In these cases the notion of raw data is broadened so that the summary statistics are regarded as the raw data. A preliminary study should address the adequacy of the candidate summary statistics, in terms of the end uses of the data. For instance, a variable that can assume only positive values may have a distribution that is skewed to the left. In some cases a logarithmic or square root transformation might bring the distribution closer to normality. In this case the average of the transformed data would come closer to satisfying standard statistical assumptions than would the average of the raw data.

4.2.11.6 Software--

The objective of software QA is to ensure that calculator and computer programs perform accurately. Such operations should introduce no more than negligible error (e.g., 1 percent or less) relative to the intrinsic variation in the measured processes. For manual calculations, an example should

be given in which actual raw data are transformed and can be checked by reviewers. If a programmable calculator is used in this process, a copy of the programs used should be provided.

Computer programs should be designed to expedite validation. Programs should be modular, structured, well documented, logical, and should liberally employ comment statements. The use of widely available statistical analysis packages such as SAS, BMD, SPSS, and MINI-TAB is recommended, as opposed to writing analysis programs in FORTRAN, BASIC, or PL/I code. Such packages are heavily used; therefore errors have been largely eliminated, and standard documentation is widely available. Software GLPs may be found in the EPA ADP System Documentation Standards.⁵⁴

The following minimal documentation is sufficient for computerized data manipulation or analysis:

1. Reference to system documentation (some software packages supply this automatically);
2. A copy of the calling program and resulting output;
3. A concise, clearly written description of the operand data set and how it derives from the raw data and the operation or analysis to be performed; these may be embedded in the beginning of the program as a comment statement; and
4. A data dictionary defining the variables as they pertain to the operation or analysis as described in item 3 above; the data dictionary may be embedded in 3.

Compliance with items 1 through 4 has no implications for validity of the analyzed data (see Section 4.2.11.4) or appropriateness of the statistical methodology employed; they must each be addressed separately.

4.2.11.7 Data Analysis--

At every phase of a research study, from initial design to final analysis and reporting, there should be at least one mathematical model that is tentatively entertained for the data. Statistical models are a prerequisite to proper experimental design and are necessary for statistical analysis. The models should be written with the underlying assumptions clearly stated. When evidence points to modification of the models or adoption of different models, the changes and rationale should be documented.

Statistical analysis usually involves the use of study data for estimation of model parameters. These estimates may be put to a variety of uses, depending on the study objectives required and the tastes of the data analysts. If the objectives have been expressed as formal hypotheses, then statistical tests may be based on parameter estimates. If estimation rather than inference is the goal of the study, then a confidence interval approach to summarization may be adopted. In either case, the estimates are acknowledged to contain error, due to intrinsic variation and/or factors neglected by the model.

The approach of hypothesis testing is to ask whether the deviation of an estimate from a given hypothesized value or range of values is plausibly due to chance alone. If study data are sufficiently improbable in the light of a hypothesis, then the hypothesis may not be further entertained. Probabilities must also be dealt with, in an inverse sense, to construct a confidence interval; i.e., a range which contains the true value of a parameter with a certain probability.

For the statistician/data analyst, whose ultimate measurements are probabilities or functions of them, questions of accuracy of measurements become questions of accuracy of these probabilities. If the model is correct, then so are the probabilities. This is an oversimplification, of course, since there is no such thing as a totally correct model.⁵⁵ A model is a theoretical construction intended to (approximately) represent reality. In most cases we have only our observations and lack the detailed schematic that would allow complete evaluation of the model. To put it another way, the infinite sample size necessary for total model validation is lacking. This illustrates a common problem for the quality assurance of scientific research: True reference values are not available, and accuracy, in the sense of closeness to the correct value, cannot be determined.

However, a well-defined model does have numeric consequences that can be checked against the data. Such checks fall under the general rubric of goodness-of-fit tests and are the statistician's main tool for the QC of his own measurement process. As a general rule, if it can be seen from the data that a model assumption is false, then corrective action is required.

Some specific techniques for checking agreement between the model and data include inspection of plots of observed and expected values or residuals, goodness-of-fit tests for probability distributions, overfitting, and analysis of replicates. Goodness-of-fit tests include chi-squared tests for probability densities or discrete distributions of specified form and the Kolmogorov-Smirnov test for the cumulative distribution function.⁴⁹ Overfitting involves viewing the tentative model as embedded in a larger family of models and testing within the larger family whether or not there is significant evidence against the restricted (tentative) model. Ideally the larger family is defined on the basis of suspicion of how the tentative model might fail. For instance, in calibration problems where a straight line through the origin is sometimes assumed ($y = ax + \text{error}$), the model $y = ax + b + \text{error}$ may be used to represent certain types of departures. For regression problems, repeated (replicate) observations at fixed conditions allow variance estimation, independent of any model. Also, it is generally possible to estimate variance as a consequence of the model. The two variance estimates should be consistent if the model is approximately correct.

4.2.11.8 Reporting--

The most visible product of a research task is the report of significant findings. Publication guidelines applicable to the HERL research reports are available^{56 57} and minimum technical contents for nonclinical laboratory reports and health effects research have been promulgated¹³ and are shown in Figure 4-9.

The report should be concise, complete, and consistent with standard EPA formats.^{56 57} Discussion of the important technical aspects of the research should be adequate to permit qualified professionals to repeat the work. Adequate data should be included to permit at least partial calculation of important results. The conclusions drawn from the data and the rationale behind those conclusions should be clearly stated. Graphical and illustrative data correlation with supporting tables should be used whenever possible. Well-defined error estimates should be included with all quantitative values reported.

1. Name and address of the facility performing the study and the dates on which the study was initiated and completed.
2. Objectives and procedures stated in the sponsor-approved protocol, including any changes in the original protocol including justification(s).
3. Statistical methods employed for analyzing the data.
4. The test and control substances identified by name, chemical abstract (CAS) number or code number, strength, purity, and composition or other appropriate characteristics.
5. Stability of the test and control substances under the conditions of administration and storage.
6. A description of the methods used.
7. A description of the test system used. Where applicable, the final report must include the number of animals used, sex, body weight range, source of supply, species, strain and substrain, age, and procedures used for identification.
8. A description of the dosage, dosage regimen, route of administration, and duration.
9. A description of all circumstances that may have affected the quality or integrity of the data.
10. The name of the study director, the names of the other scientists or professionals, and the names of all supervisory personnel involved in the study.
11. A description of the transformations, calculations, or operations performed on the data; a summary and analysis of the data, and a statement of the conclusions drawn from the analysis.
12. The signed and dated reports of each of the individual scientists or other professionals involved in the study.
13. The locations where all specimens, raw data, and the final report are to be stored.
14. The final QA report should be prepared and signed by the quality assurance unit.

Figure 4-9. Minimum technical report content for EPA health effects tests.¹³

The presentation of results should delineate the functional relationship between the raw data and the tables or graphs and be understandable to nonstatisticians. Since most scientific studies fall short of complete representativeness, useful conclusions usually require generalizations that tend to lie outside the realm of strict statistical justification. Thus, the reader of the technical report should be informed of the statistical and physical justification supporting each conclusion. The purpose(s) and conclusion(s) of the research should be stated clearly. The estimated errors, as well as the limits of applicability of results, should be stated in such a way as to minimize misinterpretation. Application of the results to alternative theories (models) should be provided, with indication of the rationale used in reaching the stated conclusions rather than the alternative conclusions.

QC and QA activities should be detailed to permit the specialist and nonspecialist to assess correctly the level of the QA effort invested in the research. Subjective evaluation of the validity of the reported results and conclusions should be possible from the data presented.

4.2.12 Internal QC Checks

The ability of the total data system to produce data of a specified quality should be regularly evaluated to determine if corrective action (see Section 4.2.16) is needed. Internal audits, conducted by the operating group or organization, are used to obtain data for this evaluation.

EPA defines two types of audits.^{23 52} A quantitative measure of the quality of the data produced is usually obtained through a performance audit; a qualitative assessment of the ability of a system to produce data of the specified quality is evaluated through a systems audit.

In either situation, the program and rationale for internal audits should be designed based on individual components of the specific measurement process and clearly planned for and budgeted into the task plans. By using internal audits, the project officer will be able to objectively evaluate data quality as the task progresses. A detailed description of all internal QC checks should be included in the research protocol or the QA Project Plan.

4.2.12.1 Performance Audits--

Performance audits should be performed by qualified technical personnel not routinely involved in the specific task measurement process being audited. Frequently, the performance audit can only be designed to evaluate a part of the total data system, such as sampling, analysis, and/or data reduction. In such a case, the audit should be designed to evaluate each subsystem to the fullest extent possible. For example, for the Ames/Salmonella assay, an audit could be performed by introducing several mutagens of known response into the assay system. The identity of the test sample or samples would be known only to the auditor. The same principle may also be applied to analytical instrumentation. In each case, the audit values are compared with those generated by the data system(s), and conclusions are drawn to infer the quality of the data being generated by the total system.

Performance audits are generally conducted using:

1. Reference materials, for accuracy determinations, are available from several sources,^{40 43 58} most notably the National Bureau of Standards. These may be included for analysis in various types of measurement systems at relatively low cost with little interference to the normal laboratory routine and with the highest possible degree of confidence.
2. Reference devices may be obtained for which the critical parameters are known to the auditor but not the analyst. These may be more disruptive of laboratory operations and there is no possibility of anonymity of the sample; however, the final result is still a measure of the performance of the total analytical system, including the operator.
3. Cooperative analyses, such as round-robin analyses, are useful for estimating the precision of a measurement among several different operators and/or laboratories. Accuracy of the measurement can only be assessed if the analyte is a reference material.
4. Side-by-side analyses, or collaborative analyses, may be used if important variables are not controllable in the sample.

Specific internal QC checks may be employed within the sampling or analytical process to determine the bias and imprecision of specific project methodology. Several examples of specific QC checks are described below. Where applicable to HERL research projects, they should be discussed in the QA Project Plan or the research protocol.

4.2.12.1.1 Replicates--Repeated but independent measurements of the same sample by the same analyst at essentially the same time and under the same conditions are called replicates. Care should be exercised in considering replicates of a portion of an analysis and replicates of a complete analysis. For example, duplicate titrations of the same digestion are not valid replicate analyses, although they may be valid replicate titrations.²³

4.2.12.1.2 Spiked samples--Spiked samples are environmental samples to which a known quantity of a given analyte has been added in order to evaluate matrix effects. When spiked samples are analyzed concurrently with correspondingly unaltered samples, it is possible to determine if there are components in a sample that bias measurement values. Results of such analyses are often expressed as percent recovery and may be used to correct unaltered sample results to obtain "true" or correct values.²³

4.2.12.1.3 Split samples--To determine the variance between observations (replicability), between analysts or instruments in a laboratory (intralaboratory variance), or more commonly between laboratories (interlaboratory variance), a quantity of homogeneous material is split into two or more portions that are analyzed independently. The split-sample technique may be used to determine analytical method variance in these three instances, or it may be used to determine comparability of different analytical methods. The split-sample technique is often employed when there are no reference materials available; in such cases, the mean of reported results, recalculated after exclusion of outliers and technically flawed data, is often represented as the "target" or reference value, which is then used to determine the bias of individual reported values.

4.2.12.1.4 Blanks--A basic principle of the scientific method is that the baseline or nonperturbed state must be well characterized if a change from baseline state is to be accurately observed. In chemical analysis, the blank is often a pure sample component (e.g., distilled water) that does not give a positive measured response. Chemical blanks can be classified as reagent blanks or total method blanks.

- Reagent blanks--The first step the analyst must take is to determine the background of each of the reagents used in a given method of analysis. The conditions for determining the background must be identical to those used throughout the analysis, including the detection system. If the reagents are found to contain substances that interfere with a particular analysis, they should be treated to remove interferences or other satisfactory reagents must be found.^{23 35}
- Method or analytical blanks--After determining the individual reagent blanks, the analyst must determine if the cumulative blank interferes with the analyses. Determination of a method blank is accomplished by following the normal analytical procedure, step by step, including all of the reagents in the quantity required by the method. If the cumulative blank interferes with the determination, steps must be taken to eliminate or reduce the interference to a level that will permit this combination of reagents to be used. If the interferent cannot be eliminated, the magnitude of the interference must be corrected for when calculating the concentration of specific constituents in the samples being analyzed.³⁵

A method or analytical blank should be determined for each analytical procedure. The actual number of blanks analyzed is determined by the method of analysis and the number of samples being analyzed at a given time. In some methods, such as automated analytical procedures, the method blank is automatically and continuously compensated for by a continuous flow of reagents passing through the detector. In other procedures, such as gas chromatographic determination of pesticides, a method blank is run with each series of samples analyzed. Analysis of one blank for every nine samples is often recommended.

In biological experiments, the term control is analogous to the method or analytical blank described for chemical analysis. The control is an organism or part of an organism that is handled in a manner identical to the experimental group, except that it does not receive the treatment hypothesized to cause the response of interest. Comparison of responses of experimental subjects with those of controls is essential to establish levels of significance for observed results. A statistician should be consulted to determine the number of blanks or controls necessary to meet project goals.

4.2.12.1.5 Internal standards--The method of internal standards is often employed in the analysis of environmental or biological samples to

compensate for possible matrix effects. In this method, a species different from, but very similar in analytical response to, the analyte of interest is added in a fixed and known amount to all samples and standards analyzed (including calibration standards). The analytical response of both the analyte of interest (R_A) and of the internal standard (R_{IS}) is recorded for each sample or standard and the ratio of these responses (i.e., R_A/R_{IS}) is used to obtain quantitative estimates of the amount of analyte present. This method also minimizes errors due to minor fluctuations or variations in experimental conditions between individual analyses (e.g., instrumental or electronic instability, changes in environmental conditions, minor variations in instrumental settings or configuration). The basic assumption required is that matrix effects and minor experimental variations will influence the analytical responses of the analyte and the internal standard in a very similar, if not identical, manner.

Internal standards can be prepared from any stable, well-characterized materials that have the desired properties described above. It is important that they be easy to add uniformly and precisely and that no appreciable amount (free or combined) be present in the samples under investigation prior to addition of the internal standard. Examples of appropriate internal standard materials include:

- Chemical or biological samples that have been thoroughly characterized by repeated, independent analyses.
- Chemical or biological materials validated against known reference materials.
- Validated reference materials, including NBS-SRMs (see Appendix A).

4.2.12.1.6 Quality control samples--QC samples are samples containing known and verified concentrations of the analyte of interest that are prepared independent of calibration standards and are analyzed at frequent intervals throughout routine analysis. Such analyses provide continuous internal evaluation of the measurement process. If practical considerations do not prohibit the practice, QC samples should be inserted by laboratory management into the usual routine analytical stream of samples without the knowledge of the analyst(s). In this way, more objective evaluation of everyday performance can be assured. QC standards may be prepared from

materials suitable for calibration standards (Section 4.2.8). If no reliable sources of QC samples can be identified for a given project, samples routinely analyzed can be split and the duplicates analyzed independently (see Section 4.2.12.13). However, such analyses provide information on precision only and not bias.

4.2.12.1.7 Surrogate samples--In the course of testing, it may be impossible or prohibitively expensive to measure a variable of interest. In cases where a relationship (ratio) can be established between the variable of interest and a second variable that is easier to measure, the second variable can be measured as a surrogate sample. An example is the measurement of coliform bacteria as a surrogate for measurement of fecal pathogens in polluted waters.

4.2.12.1.8 Calibration standards--Calibration standards should be of the highest quality available, fully characterized, and, where possible, should be traceable to NBS standards. A detailed discussion of calibration standards and procedures is given in Section 4.2.8.

4.2.12.1.9 Control charts--When there is a repeated measurement of the same material, such as a reference material, or replicate measurements of similar samples, this information can be conveniently presented and analyzed for QC purposes using control charts (see Figure 4-10).²⁰ Samples of fixed size are taken periodically from the process, and some measures of central tendency (e.g., mean, $\bar{X}$) and dispersion (e.g., range, $\bar{R}$) are plotted against time. If these measures are far from a target value, it is suspected that the process is out of control. At this point, the process may be interrupted and a search for assignable cause begun.

The $\bar{X}$ chart and R chart procedures may be implemented with relative ease.⁵⁵ The $\bar{X}$ chart approach will declare a process out of control with respect to a target value if

$$\left| \bar{X}_i - \mu \right| > KS ,$$

where K is a constant (frequently, $K = 3$), S is the standard error of the mean $\bar{X}_i$ of the sample (as estimated from historical data), and μ is a target value. The R chart approach will declare the process out of control with respect to variability if the range (R) of the sample deviates from a target

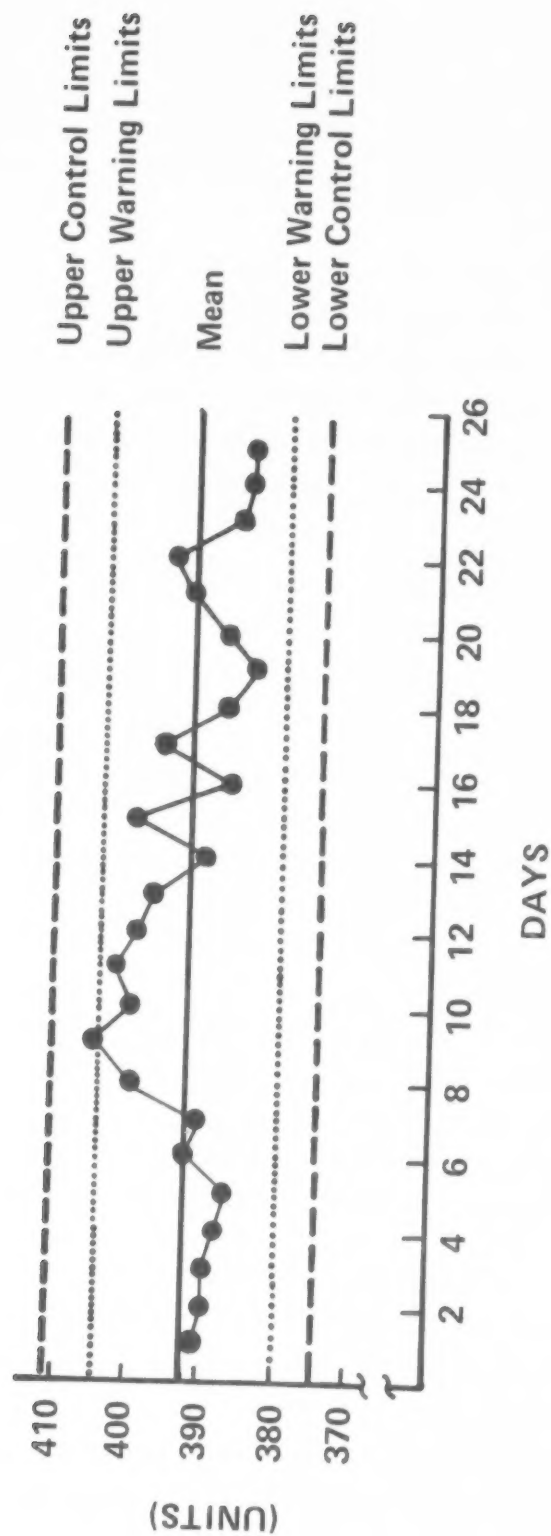


Figure 4-10. Sample $\bar{X}$ control chart.²⁰

value derived from past data by more than $3\hat{\sigma}_R$, where $\hat{\sigma}_R$ is the standard deviation of R estimated from data or computed from a standard value for the process standard deviation.

Once established, these control charts can be maintained by the laboratory personnel performing the measurements. In addition to showing graphically extreme variations in the measurement process, such charts give useful information on trends in a measurement process over time.^{20 35}

4.2.12.1.10 Reagent checks--All chemicals, biological organisms, and equipment used in an experiment should be of a quality necessary to meet project goals. The desired level of quality must be specified in the research protocol and QA Project Plan. There should be a well-established and well-documented program for screening chemicals, animals, and equipment when they are received from the supplier, and procedures for recertification of unstable reagents should also be developed where appropriate (see Section 4.2.4.4).

4.2.12.2 Systems Audits--

Internal systems audits are initiated by personnel within the organization performing the research, but are conducted by individuals not directly involved in project activities. A professional qualitative evaluation, resulting from observations of and discussions with project personnel, is made of the capability of a data system (including instruments, personnel, organization) to produce the specified data quality. Use of checklists or written questionnaires covering QA/QC items listed in Figure 4-1, as appropriate, is recommended to allow for a more complete, objective assessment during the systems audit.

The purpose of a systems audit is to provide constructive evaluation of measurement process data quality and to identify areas where improvements can be made. If this intent is followed by auditors and made clear from the beginning, project personnel will be more likely to cooperate in audit and corrective action procedures.

Systems audits are particularly useful for evaluating overall quality in measurement programs where no reliable quantitative probes exist for conducting performance audits. In general, it is recommended that if resources permit, a systems audit be conducted prior to the initiation of

any measurement program to evaluate the capability of the system for producing data of the quality required by the program objectives.

4.2.13 External Quality Assurance for Research Projects

For measurement activities supported by HERL, objective evaluation of task performance and adherence to research protocols, work plans, and QA Project Plans are accomplished through periodic audits by external nontask personnel. Such audits may be initiated at the request of the project officer, the QA officer, or the QAMS. They may be conducted on new projects requisite to funding, or on ongoing projects, either in response to identified problems in performance or as part of a routine evaluative program.

4.2.13.1 External Performance Audits--

Quantitative measurements and comparisons provide the best objective estimates of data quality. The performance audit directly evaluates the measurement aspects of the laboratory research operation being audited. The laboratory is usually given samples to be analyzed and their results are compared to expected results and judged for accuracy and precision. A pivotal issue in the proper interpretation of audit results is whether or not high quality reference standards are available (see Section 4.2.8.1).

The National Bureau of Standards has developed a series of environmentally related Standard Reference Materials (NBS-SRMs).^{40 44} A current catalog of NBS-SRMs may be obtained from:

Office of Standard Reference Data
National Bureau of Standards
Washington, DC 20234.

In addition, the World Health Organization maintains information on worldwide sources of biological standards.⁵⁸

Appropriate use of available reference materials by the auditor can provide an objective measure of specific parameter data quality. Unfortunately, for many environmentally related measurements in HERL research projects, reliable reference materials do not exist for assessment of accuracy (i.e., deviation from a true value). However, in these cases, estimates of analytical variability (precision) can still be obtained.

After completion of the performance audit, it is useful to present the results to the audited laboratory for review. This review can be a starting

point for cooperative identification of sources of measurement weakness and subsequent corrective action.

4.2.13.2 External Systems Audits--

Systems audits consist of an evaluation of the various components of a research operation, principally through inspection, and may be conducted on any research or monitoring project. The first step of a systems audit is an investigation of the laboratory's activities via inspection of protocols, standard operating procedures, proposals, reports, and scientific publications. After inspection of these materials and contact with key laboratory personnel to clarify questions, an onsite inspection may be performed. The onsite systems audit consists of inspection of facilities and operations, interviews with laboratory personnel, and reviews of key operations and documentation. The systems audit may be scored using a checklist comparing actual laboratory practices with some standard such as FDA or proposed EPA GLPs.^{13 18}

The objective of the onsite qualitative systems audit is to assess and document: facilities; equipment; personnel; recordkeeping; data validation and management; operation, maintenance, and calibration procedures; and reporting aspects of the total QC program for a project. The review should:

- Identify existing system documentation; i.e., maintenance manuals, organizational structure, operating procedures.
- Evaluate the adequacy of the procedures as documented.
- Evaluate the degree of use of and adherence to the documented procedures in day-to-day operations, based on observed conditions and a review of applicable records on file.

From qualitative measures of data quality, an auditor independent of the task organization can assess the suitability of the facilities and operations to meet project goals and identify specific areas where corrective actions may be implemented.

4.2.14 Preventive Maintenance

To ensure long-term data quality in a cost-effective manner, a rational preventive maintenance program must be followed.²³ This assumes importance roughly in proportion to the amount of instrumental data recorded. For both

routine measurement programs and basic research efforts, an effective preventive maintenance program minimizes and controls equipment downtime and therefore extends the completeness of the data. The preventive maintenance program should include scheduling, performance, and recordkeeping.

Scheduling of preventive maintenance should be developed based on the effect of equipment failure on overall data quality, any relevant site-specific effects, and equipment reliability. Extended laboratory use of specific items can be scheduled with higher reliability than if maintenance occurs only following equipment failure. This schedule should be available to the personnel performing the maintenance as well as the personnel using the equipment.

Preventive maintenance should be performed by qualified technicians, using accepted, documented procedures. These procedures should be written as SOPs and included in the QA Project Plan, research protocol, or work plan either in full or by reference. Copies should be on file with the project officer and with key project personnel. The specific service should be based on the considerations noted in the preceding paragraph and should be known to both the user and maintenance groups. A predefined set of data should be obtained before and after the maintenance activities to permit equipment performance evaluation. Calibration (see Section 4.2.8) should be performed following all major maintenance activities.

Documentation of all maintenance activities--scheduled or not--is essential to monitoring and documenting data quality. A bound notebook (see Section 4.2.4.3) should be kept with each instrument as a record of its maintenance history. A detailed description of all adjustments made and parts replaced should be recorded. If the notebook is the multicopy type, one of the copies should be kept by the maintenance group for analysis. This analysis may include such considerations as mean time between failures (MTBF) for specific components, MTBF analysis for total systems (individual and laboratory-wide), and development of an onsite spare parts inventory to cost-effectively reduce equipment downtime. Where possible, checklists should be used to ensure and document thoroughness of maintenance activities.

4.2.15 Specific Routine Procedures for Assessing Data Quality

For each major measurement variable, including all pollutant measurement systems, the QA Project Plan or research protocol must describe the routine procedures used to assess the imprecision, bias, and completeness of the measurement data. These procedures should include the equations used to calculate imprecision, bias, and completeness, and the methods used to gather data for the imprecision and bias calculations.

At the heart of the Agency QA program is the realization that measurements necessarily contain error, and that the magnitude of such errors should be estimated. This same logic applies to estimates of imprecision and bias, which should not only be reported, but should be accompanied by confidence intervals at a stated confidence level. An approximate $100(1 - \alpha)\%$ confidence interval for bias in the one-sample case is given by $(\bar{y} - T) \pm ts/\sqrt{n}$, where n is the sample size and t is the upper $100(1 - \alpha/2)$ percentage point for a t distribution with $n-1$ degrees of freedom. An approximate $100(1 - \alpha)\%$ confidence interval for squared imprecision (σ^2) is $[(n-1)s^2/\chi^2(n-1, \alpha/2), (n-1)s^2/\chi^2(n-1, 1-\alpha/2)]$, where $\chi^2(m, c)$ is the upper $100c$ percentage point of a chi-square variable with (m) degrees of freedom.⁴⁹

Formulas for confidence intervals for bias and precision parameters in regression situations can be found in standard statistics references.⁴⁹ The special case of simple linear regression is also covered by Hunter⁴⁷ (see Section 4.2.8.3). An example of this case is provided in Appendix B. Formulas for other situations should be determined in consultation with a statistician.

There should be an explicit statement made of how the QC and QA data are stored and how they are used in evaluating overall project data quality. The project officer should include appropriate results from: (1) internal performance audits (Section 4.2.12.1), (2) external performance audits (Section 4.2.13.1), and (3) calibration checks (Section 4.2.8).

4.2.16 Feedback and Corrective Action

For each project, a system for detecting, reporting, and correcting problems that may be detrimental to data quality must be established. The feedback and corrective action system chosen should accommodate the need for

quick response, thorough communication, and documentation of the problem and its solution.

The first priority in establishing a corrective action system for a project is to clearly define the management line authority for dealing with all corrective action issues. This line authority should be shown in the project organization chart (Section 4.2.3.1) or in a separate chart depending on the complexity of the research project. The assignment of authority for authorization and approval of the corrective action (once the action has been taken) should be clearly defined for each major measurement method.

The project officer should also hold regular summary briefings with technical personnel to discuss problems encountered in the research project and to make the project personnel aware of how their individual contributions to the project affect overall data quality. Such briefings should take place during the initial project planning phases and should be continued periodically throughout the duration of the project.

These activities provide an excellent opportunity to establish and maintain active employee-management feedback. Since bench-level personnel should be the best observers of routine task operations, they are the most likely to detect disturbances that may affect data quality. With effective feedback, management can quickly become aware of fluctuations that might otherwise go undetected.

Additional feedback systems should be established when facilities, equipment, or supplies are in common use by several researchers. For example, the discovery of an impure substance by one investigator should be communicated at once to all other users of the particular substance. This can be facilitated by the use of central stockroom records. Or, if a shipment of animals is found to be diseased by the Animal Care Coordinator and contamination of other test animals may result, the Animal Care Coordinator should notify all researchers using the animal care facility of the possible problems.

A description of all problems detected, the solutions devised, corrective actions taken and estimates of the effect of the problems on data quality should be made available to appropriate management in regular written QA reports (Section 4.2.17). The timing of these reports should be established based on the duration and nature of the research project.

4.2.17 QA Reports to Management

To allow routine evaluation of data quality, provision for adequate QA reporting must be made for all intramural and extramural environmentally related measurement programs. It is the responsibility of the project officer and the QA officer to establish QA reporting requirements for individual extramural projects prior to project initiation. For intramural tasks, QA reporting requirements must be included in each QA Project Plan at the division, branch, section, or group level. These requirements should be established by the appropriate functional manager (i.e., division director, branch or section chief, or group leader) in consultation with the QA officer.

Projects of short duration (1 year or less) may require only a final QA report. Projects of longer duration may require periodic (e.g., quarterly) QA reports. It is recommended that QA reports be separate from other required project reports. They should contain such information as:

- Changes in the QA Project Plan
- Significant data quality problems and status of corrective actions
- Results of performance audits
- Results of systems audits
- Results of interlaboratory or other cooperative studies
- Assessment of data quality in terms of precision, accuracy, completeness, representativeness, and comparability, where appropriate
- Quality-related training efforts

Work is currently underway within the HERL QA organization to establish Laboratory-wide QA reporting guidelines and to incorporate routine QA reporting into the existing computerized Management Information System.

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APPENDIX A

SELECTED NATIONAL BUREAU OF STANDARDS STANDARD REFERENCE MATERIALS

Source: National Bureau of Standards, NBS Standard
Reference Materials for Environmental
Research Analysis and Control, U.S. Depart-
ment of Commerce, Washington, D.C.

Clinical Laboratory Standards

These SRM's are intended for use in calibrating apparatus and validating analytical methods used in clinical and pathological laboratories, and to assist manufacturers of clinical products in meeting the chemical and physical specifications required for clinical chemicals. (For details on SRM's 930D and 931b, see Spectrophotometric Filters, page 65.)

SRM	Type	Purity %	Wt/Unit
900	Antiepilepsy Drug Level Assay	4 drugs/3 levels	Set of 4 vials
911a	Cholesterol		
912	Urea		
913	Uric Acid		
914	Creatinine		
915	Calcium Carbonate*	99.8	2 g
		99.7	25 g
		99.7	10 g
		99.8	10 g
		99.9	20 g
916	Bilirubin		
917	D-Glucose	99.0	100 mg
918	Potassium Chloride	99.9	25 g
919	Sodium Chloride	99.9	30 g
920	D-Mannitol	99.9	30 g
		99.8	50 g
921	Cortisol		
922	Tris (hydroxymethyl) aminomethane	98.9	1 g
923	Tris (hydroxymethyl) aminomethane HCl	99.9	25 g
924	Lithium Carbonate	99.7	35 g
925	VMA (4-hydroxy-3-methoxymandelic acid)	100.0	30 g
926	Bovine Serum Albumin (Powder)	99.4	1 g
927	Bovine Serum Albumin (7% Solution)	**	5 g
928	Lead Nitrate	**	10 vials, 2.15 mL ea.
929	Magnesium Gluconate	100.00	30 g
		IN PREP	10 g
930D	Glass Filters for Spectrophotometry		
931b	Liquid Filters for Spectrophotometry	+	Set of 3
932	Quartz Cuvette for Spectrophotometry	+	3 sets of 4
933	Clinical Laboratory Thermometers	+	1 each
934	Clinical Laboratory Thermometer	†	Set of 3
935	Crystalline Potassium Dichromate	**	1 each
	(UV Absorbance) Standard	(99.972)***	15 g
936	Quinine Sulfate Dihydrate		
	(Fluorescence)	(98.2)***	1 g
937	Iron Metal		
1968	Gallium Melting Point	99.90	50 g
		+++	1 ea.

*SRM 915, Calcium Carbonate, was used to develop the first referee method of analysis in clinical chemistry. This work is described in NBS Special Publication 260-36, A Referee Method for the Determination of Calcium in Serum. (See inside of back cover for ordering instructions.)

+Certified for optical properties (see p. 65.)

†Individually calibrated at 0°C and either 25, 30, or 37 °C.

††Individually calibrated at 0, 25, 30, and 37 °C.

**Conforms to NCCLS specification ACC-I.

***Apparent purity, certified for optical properties.

+++Melting Point Certified at 29.7723 °C. (See p. 61.)

Biological Standards

These SRM's are intended for use in the calibration of apparatus and methods used in the analysis of biological materials for major, minor, and trace elements.

(Values in parentheses are not certified, but are given for information only.)

SRM	Type	Wt. Unit (grams)			
1566	Oyster Tissue IN PREP	—	1571	Orchard Leaves	75
1567	Wheat Flour	80	1573	Tomato Leaves	70
1568	Rice Flour	80	1575	Pine Needles	70
1569	Brewers Yeast	50	1577	Bovine Liver	50
1570	Spinach, Trace Elements	60			

Content in µg/g (or where noted, wt %)

ELEMENT	SRM	1566	1567	1568	1569	1570	1571	1573	1575	1577
Aluminum	—	—	—	—	—	870	—	(0.12%)	545	—
Antimony	—	—	—	—	—	(0.04)	2.9	—	(0.2)	(0.005)
Arsenic	—	(0.006)	0.41	—	—	0.15	10	0.27	0.21	0.055
Barium	—	—	—	—	—	—	(44)	—	—	—
Beryllium	—	—	—	—	—	—	0.027	—	—	(0.017)
Bismuth	—	—	—	—	—	—	(0.1)	—	—	—
Boron	—	—	—	—	—	—	33	(30)	—	—
Bromine	—	(9)	(1)	—	—	(30)	—	—	—	—
Cadmium	—	0.032	0.029	—	—	(54)	(10)	(26)	(9)	—
Calcium	—	0.019%	0.014%	—	—	(1.5)	0.11	(3)	(0.5)	0.27
Cerium	—	—	—	—	—	1.35%	2.09%	3.00%	0.41%	124
Cesium	—	—	—	—	—	—	—	(1.6)	(0.4)	—
Chlorine	—	—	—	—	—	—	(0.04)	—	—	—
Chromium	—	—	—	—	—	—	(690)	—	—	(0.27%)
Cobalt	—	—	0.02	—	2.12	4.6	2.6	4.5	2.6	0.088
Copper	—	—	—	—	—	(1.5)	(0.2)	(0.6)	(0.1)	(0.18)
Europium	—	2.0	2.2	—	—	12	12	11	3.0	193
Fluorine	—	—	—	—	—	(0.02)	—	(0.04)	(0.006)	—
Gallium	—	—	—	—	—	—	(4)	—	—	—
Indium	—	—	—	—	—	—	(0.08)	—	—	(0.05)
Iodine	—	—	—	—	—	—	—	—	—	—
Iron	—	18.3	8.7	—	—	—	(0.17)	—	—	(0.18)
Lanthanum	—	—	—	—	—	550	300	690	200	268
Lead	—	—	—	—	—	(0.37)	—	(0.9)	(0.2)	—
Lithium	—	—	—	—	—	1.2	45	6.3	10.8	0.34
Magnesium	—	—	—	—	—	—	(0.6)	—	—	—
Manganese	—	—	—	—	—	—	0.62%	(0.7%)	—	604
Mercury	—	8.5	20.1	—	—	165	91	238	675	10.3
Molybdenum	—	0.001	0.0060	—	—	0.030	0.155	(0.1)	0.15	0.016
Nickel	—	(0.4)	(1.6)	—	—	—	0.3	—	—	(3.4)
Nitrogen	—	(0.18)	(0.16)	—	—	(6)	1.3	—	(3.5)	—
Phosphorus	—	—	—	—	—	(5.9%)	2.76%	(5.0%)	(1.2%)	10.6%
Potassium	—	—	—	—	—	0.55%	0.21%	0.34%	0.12%	(1.1%)
Rubidium	—	0.136%	0.112%	—	—	3.56%	1.47%	4.46%	0.37%	0.97%
Scandium	—	(1)	(7)	—	—	12.1	12	16.5	11.7	18.3
Selenium	—	—	—	—	—	(0.16)	—	(0.13)	(0.03)	—
Silicon	—	1.1	0.4	—	—	—	0.08	—	—	1.1
Silver	—	—	—	—	—	—	—	—	—	(17)
Sodium	—	—	—	—	—	—	—	—	—	(0.06)
Strontium	—	8.0	6.0	—	—	87	82	—	—	0.243%
Sulfur	—	—	—	—	—	37	44.9	4.8	—	(0.14)
Tellurium	—	—	—	—	—	—	(1900)	—	—	—
Thallium	—	(≥0.002)	(≥0.002)	—	—	—	(0.01)	—	—	—
Thorium	—	—	—	—	—	(0.03)	—	(0.05)	(0.05)	(0.05)
Uranium	—	—	—	—	—	0.12	0.064	0.17	0.037	—
Zinc	—	—	—	—	—	0.046	0.029	0.061	0.020	(0.0008)
		10.6	19.4	—	50	25	62	—	—	130

Environmental Standards

Analyzed Gases

These SRM's are intended for the calibration of apparatus used for the measurement of various components in gas mixtures, and in some cases for particular atmospheric pollutants. Each SRM is accurately certified and is primarily intended to monitor and correct for long-term drifts in instruments used. Each cylinder (except 1609) contained 870 liters at STP prior to certification, and thus contains somewhat less than 870 L (SRM 1609 contained 68 liters). All cylinders conform to the appropriate DOT specifications.

SRM	Type	Nominal Concentrations		
1609	Oxygen in Nitrogen	O ₂	20.95	mole percent
1658	Methane in Air	CH ₄	0.951	μmol/mol (ppm)
1639	Methane in Air	CH ₄	9.43	μmol/mol (ppm)
1660	Methane-Propane in Air	CH ₄	4.10	μmol/mol (ppm)
		C ₃ H ₈	0.976	μmol/mol (ppm)
1661	Sulfur Dioxide in N ₂	SO ₂	480	μmol/mol (ppm)
1662	Sulfur Dioxide in N ₂	SO ₂	942	μmol/mol (ppm)
1663	Sulfur Dioxide in N ₂	SO ₂	1497	μmol/mol (ppm)
1664	Sulfur Dioxide in N ₂	SO ₂	2521	μmol/mol (ppm)
1665a	Propane in Air	C ₃ H ₈	3	ppm
1666a	Propane in Air	C ₃ H ₈	10	ppm
1667a	Propane in Air	C ₃ H ₈	50	ppm
1668a	Propane in Air	C ₃ H ₈	100	ppm
1669a	Propane in Air	C ₃ H ₈	500	ppm
1673a	Carbon Dioxide in Nitrogen	CO ₂	1.0	mol %
1674a	Carbon Dioxide in Nitrogen	CO ₂	7.5	mol %
1675a	Carbon Dioxide in Nitrogen	CO ₂	15.0	mol %
1677b	Carbon Monoxide in Nitrogen	CO	10	ppm
1678b	Carbon Monoxide in Nitrogen	CO	50	ppm
1679b	Carbon Monoxide in Nitrogen	CO	100	ppm
1680a	Carbon Monoxide in Nitrogen	CO	500	ppm
1681a	Carbon Monoxide in Nitrogen	CO	1000	ppm
1683a	Nitric Oxide in Nitrogen	NO	50	ppm
1684a	Nitric Oxide in Nitrogen	NO	100	ppm
1685a	Nitric Oxide in Nitrogen	NO	250	ppm
1686a	Nitric Oxide in Nitrogen	NO	500	ppm
1687a	Nitric Oxide in Nitrogen	NO	1000	ppm
2613	Carbon Monoxide in Air	CO	18.1	μmol/mol (ppm)
2614	Carbon Monoxide in Air	CO	43.0	μmol/mol (ppm)
2619	Carbon Dioxide in N ₂	CO ₂	0.5	mol percent
2620	Carbon Dioxide in N ₂	CO ₂	1.0	mol percent
2621	Carbon Dioxide in N ₂	CO ₂	1.5	mol percent
2622	Carbon Dioxide in N ₂	CO ₂	2.0	mol percent
2623	Carbon Dioxide in N ₂	CO ₂	2.5	mol percent
2624	Carbon Dioxide in N ₂	CO ₂	3.0	mol percent
2625	Carbon Dioxide in N ₂	CO ₂	3.5	mol percent
2626	Carbon Dioxide in N ₂	CO ₂	4.0	mol percent

Analyzed Liquids and Solids

These SRM's are intended for use in the analysis of materials for elements of interest in health or environmental problems. See also: Clinical SRM's page 39, and Industrial Hygiene SRM's page 44.

SINGLE ELEMENT

Concentrations:

Weight percent — boldface

Microgram per gram — light face

Nanogram per milliliter — italics

SRM	Type	Unit Size	Lead	Sulfur	Mercury
1579	Powdered Lead Base Paint	35 g	11.87%	—	—
1620	Sulfur in Residual Fuel Oil	IN PREP	—	—	—
1621	Sulfur in Residual Fuel Oil	100 mL	—	1.05%	—
1622a	Sulfur in Residual Fuel Oil	IN PREP	—	—	—
1623a	Sulfur in Residual Fuel Oil	IN PREP	—	—	—
1624	Sulfur in Distillate Fuel Oil	100 mL	—	.211%	—
1630	Trace Mercury in Coal	50 g	—	—	0.13 $\mu\text{g/g}$
1641a	Mercury in Water ($\mu\text{g/mL}$)	IN PREP	—	—	—
1642a	Mercury in Water (ng/mL)	950 mL	—	—	<i>1.10 ng/mL</i>

SRM	Type	Element Certified	Nominal Concentration	Vol./Unit (mL)
1636	Lead in Reference Fuel	Pb	12, 20, 28 and 773 $\mu\text{g/g}^*$	3 vials each
1637	Lead in Reference Fuel	Pb	12, 20, and 28 $\mu\text{g/g}^*$	4 vials each
1638	Lead in Reference Fuel	Pb	773 $\mu\text{g/g}^*$	12 vials

*Equivalent grams per gallon are: 0.03, 0.05, 0.07, and 2.0 g/gal, respectively

MULTI-ELEMENT

Concentrations:

Weight percent — boldface

Microgram per gram — light face

Nanogram per gram — italics

SRM	Type	Unit Size	Al	As	Be
1632a	Trace Elements in Coal (Bituminous)	75 g	(1.64%)	9.3	—
1633a	Trace Elements in Coal Fly Ash	IN PREP	—	—	—
1634	Trace Elements in Fuel Oil	100 mL	—	(0.095)	(<0.01)
1635	Trace Elements in Coal (Subbituminous)	75 g	—	.42	—
1643a	Trace Elements in Water (ng/g)	IN PREP	—	—	—
1645	River Sediment	70 g	—	—	—
1646	Estuarine Sediment	IN PREP	—	—	—
1648	Urban Particulate	2 g	—	115	—

SRM	Cd	Cr	Co	Cu	Fe	Pb	Mn
1632a	0.17	34.4	(6.8)	16.5	11100	12.4	28
1633a	—	—	—	—	—	—	—
1634	(.01)	(0.09)	—	—	13.5	0.041	(0.12)
1635	.03	2.5	(0.65)	3.6	2390	1.9	21.4
1643a	—	—	—	—	—	—	—
1645	10.2	2.96	—	109	11.3	714	785
1646	—	—	—	—	—	—	—
1648	75	403	—	609	3.91	0.655	—

Industrial Hygiene Standards

Organic Solvents on Charcoal

These SRM's consist of charcoal tubes to which have been added known quantities of the specified organic solvent. Each SRM consists of eight tubes, two each of four solvent levels (except 2661a). SRM 2661a consists of nine tubes, three each of three solvent levels. Each tube is color coded for both the solvent and the solvent level.

SRM	Solvent	Solvent Color Code	Solvent level, mg per tube (Solvent Level Color Code)			
			I (red)	II (blue)	III (green)	IV (black)
2661a	Benzene	red	16*	30*	54*	
2662	m-Xylene	blue	0.040	0.293	1.79	8.38
2663	p-Dioxane	green	.016	.112	0.996	6.49
2664	1,2-Dichloroethane	white	.098	.381	1.56	5.80
2665	Chloroform	yellow	.147	.516	2.14	6.87
2666	Trichloroethylene	black	.286	1.03	4.09	15.4
2667	Carbon Tetrachloride	gold	.033	0.114	0.414	1.58

*µg per tube

Freeze-Dried Urine

These SRM's consist of two bottles of freeze-dried human urine, one containing a low and one an elevated level of the element certified.

SRM	Element	Low Level* (mg/L)	Elevated Level* (mg/L)
2671	Fluorine (F ⁻)	0.635	7.14
2672	Mercury	0.0042	0.294

*When reconstituted with 50 mL water.

Materials on Filter Media

These SRM's consist of potentially hazardous materials deposited on filters to be used to determine the levels of these materials in industrial atmosphere.

SRM	Type	Material Certified	Quantity Certified (µg. filter)			
			I	II	III	IV
2675	Beryllium on Filter Media	Beryllium	0.052	0.26	1.00	—
2676a	Metals on Filter Media	Cadmium	1.02	2.50	10.18	—
		Lead	6.96	15.23	29.64	—
		Manganese	1.97	9.89	19.70	—
		Zinc	9.86	49.52	99.22	—
2679	Quartz on Filter Media	Quartz	3.8	29.9	76.1	193.2
		Clay	(400)	(370)	(320)	(200)

Trace Element Standards

The SRM's listed below were designed for trace chemical analysis, specifically for calibrating instruments and checking analytical techniques and procedures used to determine trace elements in various inorganic matrices. In addition many SRM's certified for chemical composition have one or more constituents certified at or below the 100 μ g/g level.

Trace Element Standards (Nominal Concentrations)

Element	607 (ppm)	610-611 (ppm)	612-613 (ppm)	614-615 (ppm)	616-617 (ppm)
Antimony	—	—	—	(1.06)	(0.078)
Barium	—	—	(41)	—	—
Boron	—	(351)	(32)	(1.30)	(0.20)
Cadmium	—	—	—	(0.55)	—
Cerium	—	—	(39)	—	—
Chromium	—	(398.5)	(37.8)	(0.99)	—
Cobalt	—	(390)	(35.5)	0.71	—
Copper	—	(444)	(37.7)	1.34	(0.65)
Dysprosium	—	—	(35)	—	—
Erbium	—	—	(39)	—	—
Europium	—	—	(36)	(0.99)	—
Gadolinium	—	—	(39)	—	—
Gallium	—	—	—	(1.3)	(0.23)
Gold	—	(25)	(5)	(0.5)	(0.18)
Indium	—	—	—	(0.75)	(0.26)
Iron	—	458	51	13.5	(11)
Lanthanum	—	—	(36)	(0.83)	(0.034)
Lead	—	426	38.57	2.32	1.85
Manganese	—	485	(39.6)	(1.41)	0.62
Molybdenum	—	(422.6)	(36.94)	(0.79)	—
Neodymium	—	—	(36)	—	—
Nickel	—	458.7	38.8	(0.95)	—
Potassium	—	(461)	(64)	30	29
Rhenium	—	(49.43)	(6.67)	(0.17)	(0.004)
Rubidium	523.90	425.7	31.4	0.855	0.0998
Samarium	—	—	(39)	—	—
Scandium	—	—	—	(0.59)	(0.026)
Silver	—	(254)	22.0	0.42	—
Strontium	65.485	515.5	78.4	45.8	41.72
Thallium	—	(61.8)	15.7	0.269	(0.0082)
Tantalum	—	(447)	(44)	(0.74)	(0.025)
Thorium	—	457.2	37.79	0.748	0.0252
Titanium	—	(437)	(50.1)	(3.1)	(2.5)
Uranium	—	461.5	37.38	0.823	0.0721
Ytterbium	—	—	(42)	—	—
Zinc	—	(433)	—	(2.43)	—

In addition to the 36 elements listed above, the Glass SRM's contain the following 25 elements: As, Be, Bi, Cs, Cl, F, Ge, Hf, Hg, Li, Lu, Mg, Nb, P, Pr, Se, S, Te, Tb, Tm, Sn, W, V, Y, and Zr.

CERTIFIED PHYSICAL PROPERTIES STANDARDS

Ion Activity Standards

These SRM's are intended for use in the preparation of solutions for the calibration of specification electrodes. This includes the pH and pD measuring systems.

pH Standards

These SRM's are furnished as crystals for the preparation of solutions of known hydrogen ion concentration for calibrating and checking the performance of commercially available pH materials and instruments. They are furnished with certificates giving directions for preparation of the solutions and tables of pH values at various temperatures.

SRM's 1861c and 1861lc, 191 and 192, and 922 and 923, are certified for use in admixture only. At an equimolar (0.025 molal) mixture of SRM's 1861c and 1861lc, a pH(S) of 6.863 at 25 °C is obtained. Directions also are furnished for the preparation of a physiological reference solution from 1861c and 1861lc having a pH(S) of 7.415 at 25 °C.

SRM	Type	pH(S) (at 25 °C)	Wt. Unit (grams)
185e	Potassium acid phthalate	4.004	60
1861c	Potassium dihydrogen phosphate	6.863	30
1861lc	Disodium hydrogen phosphate		
187b	Borax	7.415	30
188	Potassium hydrogen tartrate	9.183	30
		3.557	60
189	Potassium tetroxalate	1.679	65
191	Sodium bicarbonate		
192	Sodium carbonate	10.01	30
922	Tris(hydroxymethyl)aminomethane		
923	Tris(hydroxymethyl)aminomethane hydrochloride	7.699	25
			35

pD Standards

These SRM's are furnished as crystals for preparation of solutions of known deuterium-ion concentration for the calibration and correction of pH indicating equipment to indicate pD data. SRM's 21861 and 21861I, and 2191 and 2192, are certified for use in admixtures only.

SRM	Type	pD(S) Values	Wt. Unit (grams)
21861	Potassium dihydrogen phosphate	7.43	30
21861I	Disodium hydrogen phosphate		
2191	Sodium bicarbonate	10.74	30
2192	Sodium carbonate		

Ion-Selective Electrodes

These SRM's are certified for the calibration of ion-selective electrodes and have conventional ionic activities based on the Stokes-Robinson hydration theory for ionic strengths greater than 0.1 mole per liter.

SRM	Type	Certified Property	Wt. Unit (grams)
2201	Sodium Chloride	pNa, pCl	125
2202	Potassium Chloride	pK, pCl	
2203	Potassium Fluoride	pF	

Primary, Working, and Secondary Standard Chemicals

These SRM's are high-purity chemicals defined as primary, working, and secondary standards in accordance with recommendations of the Analytical Chemistry Section of the International Union of Pure and Applied Chemistry [Ref. Analyst 90, 251 (1965)]. These definitions are as follows:

Primary Standard:

a commercially available substance of purity 100 ± 0.02 percent (Purity 99.98+ percent).

Working Standard:

a commercially available substance of purity 100 ± 0.05 percent (Purity 99.95+ percent).

Secondary Standard:

a substance of lower purity which can be standardized against a primary grade standard.

SRM	Type	Wt./Unit (grams)	Certified Use	Purity Stoichiometric
17a	Sucrose	60	Polarimetric Value	a
40h	Sodium Oxalate	60	Reductometric Value	99.95
41b	Dextrose (D-glucose)	70	Reductometric Value	b
83c	Arsenic Trioxide	75	Reductometric Value	99.99
84h	Acid Potassium Phthalate	60	Acidimetric Value	99.99
136c	Potassium Dichromate	60	Oxidimetric Value	99.98
350	Benzoic Acid	30	Acidimetric Value	99.98
723	Tris(hydroxymethyl)aminomethane	50	Basimetric Value	99.97
944	Plutonium Sulfate Tetrahydrate	0.5	Assay	100
949e	Plutonium Metal	0.5	Assay	99.996
950b	Uranium Oxide (U_3O_8)	25	Uranium Oxide Standard Value	99.968
951	Boric Acid	100	Acidimetric and Boron Isotopic Value	100.00
960	Uranium Metal	26	Assay	99.975
984	Rubidium Chloride	1	Assay and Isotopic	99.90
987	Strontium Carbonate	1	Assay and Isotopic	99.98
999	Potassium Chloride	60	Assay Standard for Potassium Chloride	99.98 99.99

^aSucrose-Moisture <0.01 percent, Reducing Substances <0.02 percent, Ash 0.001 percent.
^bDextrose-Moisture 0.07 percent, Ash 0.002 percent.

Hydrocarbon Blends

Four standard hydrocarbon blends are available for calibration of mass spectrometers and gas chromatographic procedures used in the analysis of gasolines, naphthas, and blending stocks. The even numbered SRM 596 is a virgin naphtha and the odd numbered SRM's 593, 597, and 599, are representative of typical catalytically cracked naphthas in the C₇ and C₈ paraffin and cycloparaffin series.

Each SRM is supplied in a unit of ten sealed ampoules. Each ampoule contains 0.03 mL of the blend. Each ampoule is intended to provide material for only one calibration analysis so that possible fractionation of components will be avoided.

For individual components present in the mixtures in the amount of 10% or less (by volume), the limits of error in composition are not greater than ± 0.01 percent and for components present in more than 10 percent, the limits of error are not greater than ± 0.10 percent.

SRM	593	596	597	599
Blend No.	2	5	6	8
Unit (Ampoules)	10	10	10	10
Hydrocarbon	Volume Percent (Nominal)			
n-Heptane	17	—	—	—
2-Methylhexane	25	—	—	—
3-Methylhexane	30	—	—	—
2,2-Dimethylpentane	—	—	—	—
2,3-Dimethylpentane	20	—	—	—
2,4-Dimethylpentane	—	—	—	—
Methylcyclohexane	8	—	—	—
Ethylcyclopentane	—	57	32	—
1,1-Dimethylcyclopentane	—	9	14	—
1,trans-2-Dimethylcyclopentane	—	4	3	—
—	—	14	30	—
1,trans-3-Dimethylcyclopentane	—	—	—	—
Ethylcyclohexane	—	16	21	—
1,trans-2-Dimethylcyclohexane	—	—	—	17
1,cis-3-Dimethylcyclohexane	—	—	—	7
1,trans-4-Dimethylcyclohexane	—	—	—	19
—	—	—	—	14
1-Methyl-cis-2-ethylcyclopentane	—	—	—	20
1,1,3-Trimethylcyclopentane	—	—	—	4
1,trans-2-cis-3-Trimethylcyclopentane	—	—	—	6
1,trans-2-cis-4-Trimethylcyclopentane	—	—	—	13

Metallo-Organic Compounds

These SRM's are intended for the preparation of solutions in oils of known and reproducible concentrations of metals. Because "matrix" effects occur, it is desirable to prepare the standard solutions in oil identical or similar to the oil being studied. Possession of an adequate collection of these metallo-organic SRM's permits the preparation of any desired blend of known concentrations of metal in the appropriate lubricating oil. They are primarily for the calibration of spectrochemical equipment used in the determination of metals in lubricating oil. This technique is used extensively in the defense program, the transportation industry, and other industries where the consequences of failure of a moving metal part may range from inconvenient to catastrophic.

The Certificate supplied with each SRM gives the percentage of the element of interest and directions for preparing a solution of known concentration in lubricating oil.

Constituent Certified				Type
Element	(wt. percent)	Wt. Unit (grams)		
Al	8.07	5	Aluminum 2-ethylhexanoate	
Ba	28.7	5	Barium cyclohexanebutyrate	
B	2.4	5	Menthyl borate	
Cd	24.8	5	Cadmium cyclohexanebutyrate	
Ca	12.5	5	Calcium 2-ethylhexanoate	
Cr	9.6	5	Tris(1-phenyl-1,3-butanediono)chromium (III)	
Co	14.8	5	Cobalt cyclohexanebutyrate	
Cu	16.37	5	Bis(1-phenyl-1,3-butanediono) copper (II)	
Fe	10.45	5	Tris(1-phenyl-1,3-butanediono) iron (III)	
Pb	36.65	5	Lead cyclohexanebutyrate	
Li	4.1	5	Lithium cyclohexanebutyrate	
Mg	6.45	5	Magnesium cyclohexanebutyrate	
Mn	13.2	5	Manganous cyclohexanebutyrate	
Hg	36.2	5	Mercuric cyclohexanebutyrate	
Ni	13.89	5	Nickel cyclohexanebutyrate	
P	9.48	5	Triphenyl phosphate	
Si	14.14	5	Octaphenylcyclotetrasiloxane	
K	10.1	5	Potassium erucate	
Ag	42.60	5	Silver 2-ethylhexanoate	
Na	12.0	5	Sodium cyclohexanebutyrate	
Sr	20.7	5	Strontium cyclohexanebutyrate	
Sn	22.95	5	Dibutyltin bis(2-ethylhexanoate)	
V	13.01	5	Bis(1-phenyl-1,3-butanediono) oxovanadium (IV)	
Zn	16.66	5	Zinc cyclohexanebutyrate	

Neutron Density Standard

This SRM is provided as a reference source of a cobalt-in-aluminum alloy to serve as a neutron density monitor wire SRM. Accurate determination of thermal neutron densities is essential in irradiation tests to obtain a basis for comparison of densities among reactors, in applying data in the design of reactors, in understanding the mechanisms of radiation damage, and for use in neutron activation analysis. The wire is 0.5 mm in diameter and 1 meter long.

SRM	Type	Cobalt Content (Weight percent)
953	Neutron density monitor wire (Co in Al)	0.116

Fission Track Glass Standards

These SRM's, at four uranium concentration levels, will aid fission track laboratories in interlaboratory comparisons of data and in monitoring neutron flux for irradiations. The fission track glass standards are certified for the neutron flux ($n \cdot \text{cm}^{-2} \cdot \text{sec}^{-1}$) that induced uranium fission in selected wafers. The materials were irradiated in the NBS 10 Megawatt Research Reactor, at two different neutron energies.

Each SRM unit contains four unirradiated glass wafers and two irradiated wafers.

SRM	Total U concentration ppm (by weight)	^{235}U atom percent	Irradiation time (sec.)
961	461.5	0.2376	RT-3 8
962	37.38	0.2392	RT-4 12 RT-3 8
963	0.823	0.2792	RT-4 12 RT-3 80
964	0.0721	0.616	RT-4 120 RT-3 360 RT-4 540

Isotopic Reference Standards

The isotopic composition of these SRM's has been determined by mass spectrometry, by comparison with mixtures prepared from high-purity separated isotopes. They are useful for those looking for small variations in the isotopic composition of the elements, and for the evaluation of mass discrimination effects encountered in the operation of mass spectrometers.

SRM	Isotopic Reference Standards	Element Certified	Wt./Unit (grams)
951	Boric Acid	Boron	1.0
952	Boric Acid, 95% Enriched ^{10}B	Boron	100
975	Sodium Chloride	Chlorine	0.25
976	Copper Metal	Copper	.25
977	Sodium Bromide	Bromine	.25
978	Silver Nitrate	Silver	.25
979	Chromium Nitrate	Chromium	.25
980	Magnesium Metal	Magnesium	.25
*981	Lead Metal, Natural	Lead	1.0
*982	Lead Metal, Equal Atom (206-208)	Lead	1.0
*983	Lead Metal, Radiogenic (92%-206)	Lead	1.0
984	Rubidium Chloride, assay and isotopic	Rubidium	0.25
987	Strontium Carbonate, assay and isotopic	Strontium	.25
989	Rhenium, assay and isotopic	Rhenium	pkg. (50)
990	Silicon, assay and isotopic	Silicon	wafer, 3 cm D × 0.2 cm
991	Lead-206 Spike, assay and isotopic	Lead	15
**993	Uranium-235 Spike, assay and isotopic (Solution)	Uranium	15

*Sold as a set only of three 981, 982, and 983.

**Special Nuclear forms required.

Radioactivity Standards

Information concerning the SRM appears on it or its container. A Certificate containing pertinent information on the SRM is sent under separate cover; a photocopy of the certificate is sent with the SRM. Copies of these Certificates and information concerning the applications of these SRM's are available on request to the NBS Office of Standard Reference Materials. These materials (except the carbon-14 contemporary dating standard) are shipped only by express or air freight (shipping charges collect). The prices of SRM's may change as current stocks are depleted and are replaced. Purchasers will be billed at the prices in effect at the time of shipment.

The stated accuracies of the older standards are, in general, an estimate of the standard deviation added to an estimate of maximum possible systematic error. The accuracies of more recent standards are based on the 99 percent confidence level of precision, with the same estimate of systematic error.

The International Commission on Radiation Units (ICRU) recommended definition of the activity (A) of a quantity of a radioactive nuclide is the quotient of ΔN by Δt , where ΔN is the number of nuclear transformations that occur in this quantity, in time Δt : ($A = \Delta N / \Delta t$). NBS uses the abbreviation ntps for nuclear transformation per second. In this list both ntps and dps are used; the latter when dps has been used in certificates printed before 1968. The terms: α ps, β^+ ps, β^- ps, K-x-rays ps, γ ps are used for the emission rates of alpha particles, beta particles, positrons, K-x-rays, and gamma-rays, respectively.

The SRM's listed below, not marked with an asterisk (*), may be ordered singly, without a license, under the general licensing provisions of the Atomic Energy Act of 1954. Those marked by an asterisk are available only under the special licensing provisions of the Atomic Energy Act of 1954.

NOTE: Certain radionuclides are not economical to maintain in stock because of short half lives or low demand. When sufficient demand exists, based on letters of inquiry, these materials are prepared and those who have expressed interest are notified of their availability. If you need any radionuclides not listed, contact the Radioactivity Section, Room C114, Radiation Physics Building, National Bureau of Standards, Washington, D.C. 20234 (Telephone: 301-921-2668).

In addition, chemically stable solutions of most radionuclides, including those no longer issued by NBS or that are currently out of stock, may be submitted to NBS for calibration as described in "Calibration and Related Measurement Services of the National Bureau of Standards," NBS Special Publication 250 (1978). Requests for these tests should be submitted, with full source information for approval of suitability, to the Radioactivity Section.

Alpha-Particle Standards

These SRM's consist of a practically weightless deposit of the nuclide on a thin platinum foil cemented to a monel disk.

SRM	Radionuclide	Approximate Activity at Time of Calibration (Month Year)	Uncertainty (%)
*4906	Plutonium-238	IN PREP	
4904-E	Americium-241	10^1 to 6×10^1 ntps (2 70)	1.0
4907	Gadolinium-148	50 to 2×10^4 ntps (1 73)	1.7

Beta-Particle and Gamma-Ray Gas Standards

These SRM's contain the Radionuclide in the inactive gas at a pressure of about one atmosphere in a glass break-seal ampoule.

SRM	Radionuclide	Approximate Activity at Time of Calibration (Month Year)	Uncertainty (%)
4302	Argon-39	3.3 × 10 ⁴ ntps source IN PREP 5 × 10 ⁷ ntps/mole (3/74) 1 × 10 ⁷ ntps source (11/74)	1.5
4308	Krypton-85		
4935-C	Krypton-85		1.0
*4235	Krypton-85		1.0

Alpha-Particle, Beta-Particle, Gamma-Ray, and Electron-Capture Solution Standards

These standard reference materials are contained in flame-sealed ampoules.

SRM	Radionuclide	Approximate Activity or Emission Rate per gram of Solution at Time of Calibration (Month, Year)	Approx. Weight of Solution (gram)	Accuracy (%)
4229	Aluminum-26	39 ntps (11/71)	4.6	1.1
4333	Americium-243	3 ntps (9/74)		
4219-B	Cadmium-109	1 × 10 ⁵ γ ps (11/76)	5	1
4250	Cesium-134	1 × 10 ⁶ (9/77)	5	2.0
*4233	Cesium-137	5 × 10 ¹⁴ atoms (12/72)	5.0	1.1
4925	Carbon-14 (benzoic acid in toluene)	2 × 10 ⁴ dps (7/58)	5.1	0.5
4222	Carbon-14 (n-hexadecane)	4 × 10 ⁴ dps (6/67)	3	2.4
4223	Carbon-14 (n-hexadecane)	4 × 10 ³ dps (6/67)	3	3.1
4224	Carbon-14 (n-hexadecane)	4 × 10 ² dps (6/67)	3	3.1
4245	Carbon-14 (sodium carbonate)	4 × 10 ² dps (5/74)	5	3.1
4246	Carbon-14 (sodium carbonate)	4 × 10 ⁴ ntps (5/74)	5	1.0
4247	Carbon-14 (sodium carbonate)	4 × 10 ² ntps (5/74)	5	0.9
4943	Chlorine-36	1 × 10 ⁴ β ps (1962)	3	1.1
4941-D	Cobalt-57	6 × 10 ⁵ ntps (5/73)	5.1	2.3
4913-B	Cobalt-60	1 × 10 ⁵ ntps (5/75)	5	1.8
4370	Europium-152	7 × 10 ⁴ ntps (5/78)	5.1	1.1
4926-C	Hydrogen-3 (H ₂ O)	4 × 10 ³ ntps (6/78)	18	1.4
4927-B	Hydrogen-3 (H ₂ O)	7 × 10 ⁵ ntps (6/78)	3	1.2
4947	Hydrogen-3 (C ₆ H ₅ CH ₃)	3 × 10 ⁵ dps (2/64)	4	1.2
*4949	Iodine-129	0.2 μCi (1973)	1.1	1.0
4929-C	Iron-55	2 × 10 ⁴ K-x-ray ps (4/70)	3.9	1.7
*4226	Nickel-63	2 × 10 ⁶ ntps (5/68)	4.1	2.7
4331	Plutonium-239	6 α ps (3/75)	2	1.0
4940-B	Promethium-147	5 × 10 ³ ntps (2/76)	3	1.0
4228-B	Selenium-75	1 × 10 ⁶ ntps (4/74)	5	1.9
4922-E	Sodium-22	2 × 10 ⁵ β ps (3/67)	5.1	2.9
4919-D	Strontium-Yttrium-90	4 × 10 ³ ntps (4/75)	2.9	1.4
4234	Strontium-Yttrium-90	1 × 10 ⁶ ntps (8/75)	3.1	2.1

Contemporary Standard for Carbon-14 Dating Laboratories

SRM	Description
4990	Oxalic acid; no specific activity is given. (One pound of oxalic acid taken from specially prepared material for use as a common contemporary standard against which world-wide measurements can be compared.)

NOTE: In Preparation.

SRM	Radionuclides	Environmental Standards			
		Approximate Activity, or Emission Rate, per gram, at Time of Calibration (Month Year) (s ⁻¹ g ⁻¹)	Form	Approx. Mass (g)	Overall Uncertainty (%)
4350	Certified ⁴⁰ K, ⁵⁴ Mn, ⁶⁰ Co, ⁶⁵ Zn, ⁹⁰ Sr, ⁹⁰ Y, ¹³⁷ Cs, ¹⁵² Eu, ¹⁵⁴ Eu, ²²⁸ Ac, ²³⁹ Pu, ²⁴⁰ Pu Values given, but uncertified ⁵⁵ Fe, ¹²⁵ Sb, ¹⁵⁵ Eu, ²⁰⁸ Tl, ²¹² Pb, ²¹² Bi, ²¹⁴ Pb, ²¹⁴ Bi, ²²⁶ Ra, ²²⁸ Th, ²³⁰ Th, ²³² Th, ²³¹ Pa, ²³⁴ U, ²³⁵ U, ²³⁸ U, ²³⁸ Pu, ²⁴¹ Am, ²⁴⁴ Cm	1 per radionuclide (1-75) 1 per radionuclide	River Sediment River Sediment	100 100	varies NA
RM45b	Contains the same radionuclides at SRM 4350 at <i>approximately</i> equal concentrations. No values provided.				

Low Energy Photon Sources**

SRM	Radionuclide	Approximate Emission Rate (Month Year)	Uncertainty (%)
4260-B	Iron-55	1 to 2 × 10 ³ kxs ⁻¹ steradian (4/77)	1.8
4261	Cadmium-109	10 ³ kxs ⁻¹ (6/76)	1.5
4264	Tin-121m	200 to 750 - 37.15 keV γ s ⁻¹ (5-71)	3.0

**These SRM's consist of a thin-layer deposit of the radionuclide on a thin stainless steel or platinum foil cemented to a monel disk.

Gamma-Ray "Point-Source" Standards

This group of Standard Reference Materials is usually prepared by depositing the radioactive material and sealing it between two layers of polyester tape, mounted on an aluminum ring. Exceptions to this procedure are americium, krypton, and thorium SRM's. The americium-241 SRM's, 4211 and 4213, are prepared by electroplating americium onto a 0.010-cm thick platinum foil, which is covered with a 0.005-cm thick aluminum foil. The aluminum-covered source is sandwiched between two layers of 0.036-cm thick polyurethane film tape. The krypton-85 SRM, 4212, is prepared by sealing a krypton-85 impregnated aluminum foil between two glass disks, with an epoxy adhesive. The thorium-228 SRM's, 4205 and 4206, are prepared by depositing and sealing the radionuclide between two layers of gold foil and this sandwich is then sealed between two double layers of polyurethane-film tape.

SRM	Radionuclide	Gamma-Ray Energy (mev)	Approximate Activity (ntps) at Time of Calibration (Month Year)	Uncertainty (%)
4206-B	Thorium-228	2.614	10^3 (12/76)	1.8
4218-C	Europium-152	0.122-1.408	4 to 50×10^4 (5/78)	1.4
*4211	Americium-241	0.060	4 to 18×10^4 (2/70)	2.8
*4213	Americium-241	0.060	2 to 4×10^5 (2/70)	2.8
4202-C	Cadmium-109	0.088	3 to 6×10^3 (11/76)	2.1
*4212	Krypton-85	0.514	7×10^6 to 4×10^7 (5/71)	2.6
4200-B	Cesium-137	0.662	7×10^4 (12/68)	1.3
*4207	Cesium-137	0.662	5×10^5 (12/68)	1.3
4201-B	Niobium-94	0.702, 0.871	4 to 6×10^3 (4/70)	1.5
4240	Bismuth-207	0.5696, 1.0634, 1.7697	5×10^4 to 1×10^5 (1/73)	1.4
4203-C	Cobalt-60	1.173, 1.333	1 to 2×10^5 (2/73)	1.2
4210	Cobalt-60	1.173, 1.333	2×10^6 (4/69)	1.1
4991-C	Sodium-22	1.2745	6×10^4 (4/69)	1.5
4996-B	Sodium-22	1.2745	3×10^5 (4/69)	1.5

Radium Gamma-Ray Solution Standards

These samples are contained in flame-sealed glass ampoules.

SRM	Radium Content (in micrograms)	Uncertainty (%)
4955	0.1	± 3.6
4956	0.2	4.4
4957	0.5	1.8
4958	1.0	1.8
4959	2.0	1.3
4960	5.0	1.3
4961	10	1.1
4962	20	1.1
4963	50	1.1
4964-B	102	0.5

Radium Solution Standards for Radon Analysis

These samples are contained in flame-sealed glass ampoules.

SRM	Nominal Radium Content, per gram (Month Year)	Approx. Wt. Soln. (grams)	Uncertainty (%)
4951-C	10^{-11} (4/78)	10.4	1.8
4950-D	10^{-9} (4/78)	10.3	1.5
4953-C	10^{-8} (4/78)	10.3	1.3
4952-B	Blank Solution (8/76)	20	68

APPENDIX B

EXAMPLE OF CALCULATIONS THAT SHOULD BE PROVIDED
FOR ESTIMATES OF IMPRECISION AND BIAS

Linear Regression Analysis of Calibration Data

Five calibration standards consisting of sodium sulfate deposits on glass fiber filters were analyzed for sulfate mass. Letting x denote the true value and y denote the value obtained by analysis, the data (in μg sulfate/filter) are $(x,y) = (1988, 2040), (648.7, 719), (1161.5, 1170), (221.6, 222), (1504, 1640)$.

For linear regression analysis of these data, the assumed model is $y = (a + bx) + e$, with a linear systematic component $a + bx$ and random error term e having mean zero and constant variance σ^2 . Bias parameters are a and b ; σ is called imprecision. $\bar{x}, \bar{y}, S_x, S_y$ denote the averages and standard deviations of x and y , r denotes the sample correlation coefficient, n denotes sample size, t is the 100 $(1-\alpha/2)$ percentage point of a t distribution with $(n-2)$ degrees of freedom, and $\chi^2(m,c)$ in the upper 100 c percentage point of a chi-squared distribution with m degrees of freedom. For the data in this example:

$$\begin{aligned}n &= 5 & S_y &= 720.97 \\ \bar{x} &= 1,104.76 & r^2 &= 0.9954 \\ \bar{y} &= 1,158.20 & t(3, 0.975) &= 3.182 \\ S_x &= 694.75\end{aligned}$$

Formulas and recommended reporting format for summarizing linear regression analyses are shown in Table B-1. Using these formulas, estimates of bias and imprecision parameters (and their confidence intervals) for the data set in this example are shown in Table B-2.

TABLE B-1. FORMULAS AND RECOMMENDED REPORTING FORMAT
FOR SUMMARIZATION OF LINEAR REGRESSION ANALYSES

Parameter	Estimate of parameter	100 (1- α) % Confidence interval parameter
Slope	$\hat{b} = rS_y/S_x$	$\hat{b} \pm t \cdot \hat{\sigma} / (S_x \sqrt{n-1})$
Intercept	$\hat{a} = \bar{y} - \hat{\beta}_1 \bar{x}$	$\hat{a} \pm t \cdot \hat{\sigma} \sqrt{(1/n) + \bar{x}^2 / (S_x^2 [n-1])}$
Imprecision	$\hat{\sigma} = \sqrt{S_y^2(1-r^2)(n-1)/(n-2)}$	$\left(\sqrt{\frac{(n-2) \hat{\sigma}^2}{x^2(n-2, \alpha/2)}}, \sqrt{\frac{(n-2) \hat{\sigma}^2}{x^2(n-2, 1-\alpha/2)}} \right)$

TABLE B-2. ESTIMATES AND CONFIDENCE INTERVALS
FOR BIAS AND IMPRECISION PARAMETERS
OF THE FIVE-POINT CALIBRATION EXAMPLE

Parameter	Estimate of parameter	95% Confidence interval for parameter
Slope	$\hat{b} = 1.04$	(0.91, 1.16)
Intercept	$\hat{a} = 14.36$	(-149.51, 178.23)
Imprecision	$\hat{\sigma} = 56.46$	(32, 210)